Neural Correlates of Treatment in Depression and Potential Predictors of Diagnosis and Clinical Response

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Contribution towards the projects

The studies presented in Chapters 3, 4 and 5 were part of a larger project that examined the neural effects of duloxetine on the structural and functional correlates of depression. Hence, data for the above mentioned chapters were acquired from participants of the same cohort. I was involved in the day to day organization of the project in accordance with the Good Clinical Practice Guidelines. I helped in the recruitment of patients with Major Depressive Disorder and healthy controls. I screened participants through telephone interviews, conducted clinical assessments using the Structured Clinical Interviews for DSM-IV (SCID) and administered the Wechsler Adult Intelligence Scale (III). I also liaised with General Practitioners to obtain medical records of participants to ensure their eligibility in the study. I performed urinalysis, assisted with MRI scans, conducted behavioural scans while participants were in the scanner and also analysed some of the neuroimaging data for this study. Whilst in the scanner, all participants responded to four different paradigms (i.e. sad facial expressions, happy facial expressions, emotional-Stroop, and Sternberg tasks), in addition to undergoing resting state functional and structural scans. I analysed whole brain imaging data for the happy, sad and Sternberg tasks (analyses described in detail in Chapters 3 and 4). Although not part of the initial study plan, I also undertook a brief research-scholar internship at the University of Pennsylvania in Philadelphia, United States of America, to examine biomarkers of diagnosis and prognosis using machine learning techniques (Chapter 5).

For the study described in Chapter 2, participant recruitment and data collection were already completed before the commencement of my PhD. I analysed the neuroimaging data for this study and prepared the manuscript for publication.

List of abbreviations

$5HT_2$	Serotonin
ACC	Anterior Cingulate Cortex
AD	Antidepressant
ANOVA	Analysis of Variance
AUC	Area under the Curve
BA	Brodmann Area
BDI	Beck Depression Inventory
BOLD	Blood Oxygenation Level-Dependent
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBT	Cognitive Behaviour Therapy
cDAS	Control Dysfunctional Attitude Scale
CEN	Central Executive Network
COMPARE	Classification of Morphological Patterns using Adaptive Regional Elements
CSF	Cerebro Spinal Fluid
D_2	Dopamine
DAS	Dysfunctional Attitude Scale
DLPFC	Dorso Lateral Prefrontal Cortex
DMN	Default Mode Network

DRAMMS	Deformable Registration via Attribute Matching and Mutual-Saliencing
DSM-IV-TR	Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DTI	Diffusor Tensor Imaging
EM	Expectation-Maximization (Classification via clustering)
EPI	Echo Planar Images
FA	Fractional Anisotropy
FBM	Feature Based Morphometry
FIR	Finite Impulse Response
fMRI	Functional Magnetic Resonance Imaging
FWER	Family-Wise Error Rate
FWHM	Full Width at Half Maximum
GAD	General Anxiety Disorder
GLM	General Linear Model
GM	Grey Matter
HAMA	Hamilton Anxiety Rating Scale
HAMD/HRSD	Hamilton Depression Rating Scale
HV	Healthy Volunteers
IAPS	International Affective Picture System
IFG	Inferior Frontal Gyrus
IG	Information Gain

Jacob. Met. Distort	Jacobian Metric Distortion
LLE	Locally Linear Embedding
mDAS	Modified Dysfunctional Attitude Scale
MDD	Major Depressive Disorder
MICO	Multiplicative Intrinsic Component Optimization
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
NA	Not Applicable
NHS	National Health Service
NRI	Norepinephrine Reuptake Inhibitor
ODVBA	Optimally Discriminative Voxel Based Analysis
PCA	Principle Component Analysis,
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
pMDD	Psychotic MDD
RAVENS	Regional Analysis of Volumes Examined in Normalised Space
RFE	Recursive Feature Elimination
ROC	Receiver Operating Characteristic
ROI	Region of Interest

RVM	Relevance Vector Machine;
SCID	Structured Clinical Interview for DSM-IV Axis I disorders
SD	Standard Deviation
SLaM	South London and Maudsley
sMRI	Structural Magnetic Resonance Imaging
SN	Salience Network
SNRI	Serotonin Norepinephrine Reuptake Inhibitors
SPECT	Photon Emission Computerized Tomography
SPM	Statistical Parametric Mapping
SSQ	Sum of Squares of Deviations
SSRI	Selective Serotonin Reuptake Inhibitor
SVM	Support Vector Machines
TCP	Transductive Conformal Predictor
TE	Echo Time
TR	Repetition Time
TRD	Treatment Resistant Depression
TSD	Treatment Sensitive Depression
VBM	Voxel Based Morphometry
VLPFC	Ventro Lateral Prefrontal Cortex
vs	Versus
WM	White Matter

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Abstract

The works presented in this thesis examine the neural effects of treatment on different features of depression, such as affective biases, working memory impairments and dysfunctional thinking. The thesis opens with a review of longitudinal studies that examined the effects of antidepressants and psychological therapies on the neural correlates of affective and cognitive processing. Motivated by the paucity in the number of fMRI studies that examined psychotherapy in depression, Chapter 2 examines the effects of Cognitive Behavioural Therapy (CBT) on dysfunctional thinking in depression. In Chapter 3, the effects of a dual acting serotonin norepinephrine reuptake inhibitor, duloxetine, on affective biases are examined using implicit affective paradigms comprising happy and sad facial expressions. Chapter 4 investigates the neural effects of duloxetine on working memory in depression utilizing a modified version of the Sternberg Working Memory Task. Another key focus in the thesis is to examine the potential of structural neuroimaging data to identify depression and predict clinical remission using machine learning algorithms in a sample of wide ethnic diversity from the community. Findings from this study are presented in Chapter 5.

Overall, the results showed antidepressant treatment related increases in posterior cingulate during sad facial effect processing, consistent with preliminary findings that show increases in this region with antidepressants that potentiate the noradrenergic systems. The neural correlates of working memory, on the other hand, showed a significant group by time interaction during the rehearsal phase, such that there was a tendency for reductions in brain activations at the follow up scan compared to baseline in healthy controls in a network of brain areas extending from the prefrontal, to the cingulate, temporal and cerebellar regions, while no change was observed in patients. The tendency for decreased activations in controls in the follow up scan is perhaps indicative of less recruitment of these regions with increased familiarity with the task, while no change in activation in patients may reflect persistent recruitment of regions associated with working memory to maintain task performance. In the CBT study, an interaction effect was found in the left parahippocampal gyrus, which showed less attenuation in patients relative to controls at the follow up scan, perhaps reflecting an improvement in

dysfunctional thinking with CBT with some persistent vulnerability. Investigation of neuroimaging-based biomarkers in depression indicated that structural neuroanatomy combining white and grey matter distinguished patients from controls at the highest accuracy of 81% with the most stable pattern being at around 70%. In contrast, the whole brain structural correlates of depression showed limited potential as a prognostic marker. These findings suggest some distinct neural effects of treatment on cognitive and affective processing and provide preliminary evidence to indicate that identification of depression is possible within a multi-ethnic group from the general community.

1 Introduction

The important findings from this chapter have been published in two papers

1. Sankar., A & Fu, C.H (in press). Psychotherapy and Antidepressant Treatment Effects on the Functional Neuroanatomy of Depression. *Psychopathology Reviews*

2. Atkinson, L., Sankar, A., Adams, T.M., & Fu, C.H. (2014). Recent Advances in Neuroimaging of Mood Disorders: Structural and Functional Neural Correlates of Depression, Changes with Therapy, and Potential for Clinical Biomarkers. *Current Treatment Options in Psychiatry, 1*(3), 278-293.

1.1 Background

Major Depressive Disorder (MDD) is characterised by persistent depressed mood and/or a loss of interest or pleasure in activities. Additional features include fatigue, feelings of worthlessness or guilt, marked changes in weight, sleep patterns, psychomotor activity, diminished concentration, recurrent thoughts of death, suicidal ideation or suicide attempt (American Psychiatric Association, 2013). For a diagnosis of MDD to be made, the individual has to exhibit a minimum of five symptoms, and at least one of which must be depressed mood or anhedonia. The core symptoms must be present for a minimum duration of two weeks (American Psychiatric Association, 2000). The median age for onset for depression is 32 years (Kessler et al., 2005). MDD is a debilitating disorder and it is one of the leading contributors to the global burden of disease, regularly identified amongst the top five disabling conditions worldwide (Murray & Lopez, 2013).

MDD is often associated with recurrences and relapses, and the risk for relapse becomes more likely with increasing number of previous episodes (Kessing et al., 2004). It has been proposed that the processes mediating relapse grow progressively independent and are less linked to environmental stressors (Kendler et al., 2000). Hence, preventing relapse and recurrence is an essential feature in the clinical management of the disorder. At the present time, the diagnosis of major depression is based solely on clinical signs and symptoms, and there are no biological tests that are used to diagnose the disorder or to predict clinical response to a particular treatment or the course of the illness.

Diagnostic classification systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) regards depression as a consistent syndrome, in which the key focus for diagnosis is the number of symptoms that a patient presents with, which is totalled to give a sum-score (Fried & Nesse, 2015a,b). With such a classification system, often individuals with a wide range of symptoms are lumped together into one unified category. According to Shorter (2014), this is a "nosological disaster' as MDD is a very heterogeneous disorder. For instance, it is possible for two individuals who meet criteria for MDD with the DSM-V to have no symptoms in common (Fried & Nesse, 2015a). Hence, ignoring the heterogeneity of the disorder by having a broad diagnostic category

raises concerns with respect to treatment of patients with diverse symptomatic profiles (Shorter, 2014). A recent study that included over three thousand seven hundred patients with depression identified 1030 different symptom profiles (Fried & Nesse, 2015a). Examining different manifestations of the same disorder is imperative as they may have potential aetiological and/or therapeutic implications. Moreover, different symptoms are likely to have varying impacts on psychosocial functioning. Amongst the different symptoms, sad mood, difficulty concentrating and fatigue are considered most debilitating (Fried & Nesse, 2014), and therefore makes it crucial to examine different dimensions of the disorder, i.e. the affective, cognitive and somatic symptoms, rather than focussing on the total number of symptoms.

In addition, evidence from recent studies indicate that one must not consider diagnostic classification systems as a monolith for diagnosis. For example, a large multi-centre study based on 5635 adults in a major depressive episode found that, although only 16% met DSM-IV-TR criteria for bipolar disorder, 47% of them met criteria for the bipolarity specifier (Angst et al., 2011). This suggests the importance of considering factors such as family history, clinical status and illness course before making a diagnosis, especially to avoid ineffective treatment regimen (Angst et al., 2011).

An alternate approach to having a broad diagnostic label such as 'Major Depressive Disorder' has been to classify the different 'subtypes' of depression by looking for similar patterns, either in symptomology, aetiology or both. A meta-review of 754 reviews identified 15 subtypes of depression that differ on five aspects: symptom, aetiology, gender, time of onset and treatment resistance (Harald & Gordon, 2012). Unfortunately, even with such a classification system, there is still a considerable overlap between the different subtypes (Harald & Gordon, 2012),and therefore casts doubts on its utility.

The DSM, in fact, recognises some specifiers of depression that can provide more detailed information about the person's condition. Specifiers detailed in the most recent version of the DSM (i.e. version V), include MDD with anxious-distress features, mixed features, melancholic features, atypical features, catatonia, seasonal pattern, peripartum onset, and mood congruent or incongruent psychotic features (American Psychiatric Association, 2013). The differing pathophysiology of the

MDD subtypes, especially melancholic and atypical depression are extensively investigated (ex. Karlović et al., 2012; Dunjic-Kostic et al., 2013; Gold & Chrousos, 2013; Lamers et al., 2013). In general, melancholic depression is considered to be a more severe form of MDD with biological origins (Maes et al., 1991; Lamers et al., 2013), and patients with melancholic features are likely to respond better to antidepressant treatment (Guelfi et al., 1995; Herschfeld, 1999) than to placebo. There is also some evidence that tricyclic antidepressants may be better in treating depression with melancholic features compared with serotonin-specific reuptake inhibitors (Perry, 1996), but this has not been widely replicated (ex. Herschfeld, 1999). While melancholic features have been considered to have good clinical outcomes with electro-convulsive therapy (ECT) (Abrams, 2002; Taylor & Fink, 2006), a much larger study on 311 MDD patients with melancholic depression and 178 patients without melancholic features concluded that melancholia was associated with poorer treatment outcomes, compared to non-melancholic features, with acute ECT, although relapse rates reduced with continuation ECT when compared to continuation medication treatment (Fink et al., 2007).

Atypical depression is usually associated with symptoms such as increased appetite, over sleeping, leaden paralysis, and interpersonal rejection sensitivity (American Psychiatric Association, 2013). However, there are no treatment options that are seen as specifically useful for atypical depression and recent studies showed that serotonin reuptake inhibitors did not sufficiently discriminate treatment outcome in patients with atypical depression compared to those without atypical features (Stewart et al., 2010; Uher et al., 2011). An improved framework that is better able to capture the heterogeneity associated with the disorder, bearing in mind the impact of the symptoms on patients' psychosocial functioning, in addition to considering factors such as history and the course of the illness prior to the current major depressive episode may be an initial step towards having personalized treatments.

In the following paragraphs, biases in affective processing, which is a common feature of depression, as well as evidence for treatment related improvements are reviewed.

1.2 Affective bias in MDD and improvements with treatment

MDD is associated with specific biases and abnormalities which may lead to the onset and maintenance of the disorder. MDD is associated with a negative affective bias in several neurocognitive domains. In particular, MDD patients show a greater recollection of negative information relative to healthy controls, such as words (Bradley et al., 1995) and facial expressions (Ridout et al., 2003). There is a selective attention towards negative stimuli in MDD (Beck, 2008), including towards negatively valenced words (Donaldson et al., 2007) and mood-congruent images (Eizenman et al., 2003), and away from positive stimuli, such as happy facial expressions (Leppänen, 2006). Furthermore, mood congruent attentional bias in depression was apparent even with some patients already on antidepressant medications (Eizenman et al., 2003). The attentional bias towards negative stimuli manifests more in anxiety disorders (such as Generalised Anxiety Disorder; GAD), while in depression, it is usually evident when the target stimuli is presented over a relatively long duration of time, allowing more extensive processing (Mogg & Bradley, 2005). With facial expressions, MDD patients have difficulties discerning affective facial expressions, namely happy and sad expressions, which contribute to the psychosocial and interpersonal difficulties that are seen in patients with major depression (Persad & Polivy, 1993). They also tend to misinterpret happy, neutral or ambiguous faces as being sad or less happy (Bourke et al., 2010). Moreover, the selective attentional bias towards negative facial expressions is evident even in recovered patients (Bhagwagar et al., 2004; Joormann & Gotlib, 2007), while the induction of a mild negative mood in recovered patients can reinstate some of the negative biases observed in acutely depressed patients (Gemar et al., 2001).

Evidence based treatments for MDD include antidepressant medications or psychological therapies or both and treatment decisions are usually based on the severity and course of the disorder, patient preference and previous response to treatment. Both pharmacological and psychological treatments have shown to alter the emotional processing bias evident in depression. A 2-week antidepressant treatment enhanced recognition of both negative as well as positive emotions in MDD patients (Tranter et al., 2009), and a single dosage of citalopram normalised the bias towards fearful faces in

MDD patients in remission (Bhagwagar et al., 2004). Even in healthy controls, a single dose of citalopram had improved their attention towards positive words though it had also increased their recognition of fearful faces (Browning et al., 2007). Likewise, cognitive bias modification techniques, involving positive interpretations of auditory stimuli using imagery, have been associated with improvements in mood and cognitive biases in medication-free MDD patients (Blackwell & Holmes, 2010). Furthermore, enhancement of the recognition of happy faces following antidepressant treatment was linked with improvements in symptoms, wellbeing and social functioning (Tranter et al., 2009), suggesting that these emotional processing biases may be a state rather than them being persistent trait-related features of depression.

In this chapter, functional neural correlates of the effects of antidepressants and psychological therapies in major depression are discussed. Furthermore, predictors of clinical response and the potential to develop neuroimaging-based markers are reviewed.

1.3 Magnetic resonance imaging in MDD

Neuroimaging studies have extensively examined brain abnormalities that are associated with depression and its subsequent modulation with treatment. The use of neuroimaging techniques in clinical psychiatry helps understand the pathophysiology underlying different mental illnesses and it also facilitates identification of neurobiological markers for such disorders. This could have potential value for optimizing treatment regimens for patients and also in identifying early markers of disease prognosis and response prediction (Fu & Costafreda, 2013).

MDD patients show both structural and functional brain alterations in regions associated with affective processing and cognitive control, primarily in the limbic and prefrontal areas (Atkinson et al., 2014). Structural Magnetic Resonance Imaging studies (sMRI) have extensively employed region-of-interest (ROI) and Voxel-Based-Morphometry (VBM) methods to investigate neuroanatomical changes in MDD patients. Functional neuroimaging studies on the other hand were

typically performed using Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT) techniques on individuals during resting state. Although, these modes of functional imaging have been effective, poor special resolution as well as contact with radioactive tracers limit frequency of scans being repeated on the same patient (ex. Greicius et al., 2007). Functional Magnetic Resonance Imaging (fMRI) methods overcome such limitations and they have been of considerable use in studying regional brain activations in MDD patients during an acute depressive episode.

fMRI studies have applied various experimental paradigms in order to examine the networks underlying the affective biases (ex. Elliott et al., 2002; Lawrence et al., 2004; Surguladze et al., 2005; Frodl et al., 2009) and cognitive impairments (ex. Harvey et al., 2005; Wagner et al., 2006; Walter et al., 2007; Fitzgerald et al., 2008; Mitterschiffthaler et al., 2008) in MDD. In order to distinguish neural features that are state-specific from trait-related ones, it is important to consider the depressive state of the MDD sample (i.e. whether patients are in an acute depressive episode, in recovery, or in remission) and whether the study is a cross sectional analysis of patients in different mood states or whether it is a longitudinal investigation of patients following treatment. For instance, fMRI studies have investigated impairments during an acute depressive episode (Harvey et al., 2005; Grimm et al., 2008; Mitterschiffthaler et al., 2008) as well as the changes following treatment (Sheline et al., 2001; Fu et al., 2004, 2007; Walsh et al., 2007; Fu et al., 2008a; Victor et al., 2010; Arnone et al., 2012). The majority of studies have examined the effects of pharmacological treatments (Sheline et al., 2001; Davidson et al., 2003; Fu et al., 2004, 2007; Walsh et al., 2007; López-Solà et al., 2010; Victor et al., 2010; Arnone et al., 2012; Rosenblau et al., 2012; Stoy et al., 2012) and to a lesser extent on the effects of psychological interventions (Fu et al., 2008a; Dichter et al., 2009, 2010; Ritchey et al., 2011; Buchheim et al., 2012; Sankar et al., 2014; Yoshimura et al., 2014). It is unclear whether the regional changes seen after treatment is specific to antidepressants or whether such changes are common across treatment methods.

Generally longitudinal fMRI studies investigating affective processing have used standardized series of facial expressions (ex. Ekman & Friesen, 1976) or emotional pictures (ex. International Affective

Picture System (IAPS); Lang et al., 1999). Emotional processing tasks used in fMRI studies are usually either implicit or explicit in nature. For example, in a task involving the presentation of emotional faces, the explicit instruction may be to identify the gender of the presented face while the emotional expression is processed implicitly, or the explicit instruction may be to identify the emotion expressed by the presented face which becomes explicit processing of the emotion. fMRI studies often use implicit rather than explicit emotional processing tasks as they are associated with greater probability of engaging key limbic regions within the MDD network, such as the amygdala (Costafreda et al., 2008). The majority of the longitudinal MDD studies have focussed on the functional correlates of treatment in response to emotional processing (Davidson et al., 2003; Fu et al., 2004, 2007, 2008a; Victor et al., 2010; Ritchey et al., 2011; Arnone et al., 2012). Other emotional processes, such as reward (Dichter et al., 2009; Stoy et al., 2012) and painful stimuli (López-Solà et al., 2010), as well as cognitive processes, such as verbal working memory (Walsh et al., 2007) and cognitive control (Wagner et al., 2010), have also been investigated.

1.4 Neural effects of antidepressant treatment on negative emotional processing in MDD

An influential model that elucidates the neural correlates of depression was proposed by Helen Mayberg (1997). The model postulates that depression stems primarily from disruptions in the cortico-limbic pathway, which constitutes three main components, the interactions among which are essential for the regulation of mood and associated behaviours (Mayberg, 1997; Mayberg et al., 1999). The proposed model consists of the dorsal component, comprising a network of neocortical (eg. dorsolateral prefrontal and inferior parietal regions) and midline limbic structures (such as cingulate, hypothalamus, hippocampus, amygdala) which mediate the attentional and cognitive impairments evident in depression (Mayberg, 1997; Mayberg et al., 1999). The ventral component comprises a distributed network of regions including the hypothalamus-pituitary-adrenal (HPA) axis, subgenual cingulate (Brodmann area 25), insula and brain stem, and are involved with the vegetative

and somatic features of the disorder. The dorsal and the ventral components have reciprocal connections within each other as well as between components via the cingulate cortex, thalamus and hippocampus (Mayberg 1997). The third component, rostral cingulate has reciprocal connections with the dorsal and ventral part of the anterior cingulate (Mayberg, 1997). According to Mayberg (Mayberg et al., 1999), there is a reciprocal relationship between the limbic and cortical regions, and depression is characterised by decreases in the dorsal cortical structures, and increases in limbic and paralimbic activity (amygdala and subgenual cingulate), mediated by disruptions in the rostral anterior cingulate. Therefore, increased activations in the limbic regions leads to dysregulated activity in the dorsal cortical regions, decreasing the ability of the latter to regulate limbic hyperactivity.

Mayberg's model (Mayberg, 1997; Mayberg et al., 1999) is shown to have implications in the diagnosis of depression and in predicting antidepressant response. It is however important to note that more recent investigations suggest that depression may not just involve altered reciprocal connections between regions in the limbic and dorsal cortical network that form a vicious cycle, as initially speculated. For instance, resting state studies in major depressive disorder indicate that depression may be associated with decreased ability to downregulate activity within the default mode network (DMN); cortical and subcortical regions that are activated during internally directed thought processing (Sheline et al., 2009; review: Whitfield-Gabrieli & Ford et al., 2012). In MDD patients, there is also evidence that show decreased functional connectivity (Zhu et al., 2012) as well as reduced correlations in the caudate (Bluhm et al., 2009) with the precuneus and posterior cingulate, core regions of the DMN, albeit with some inconsistencies, with findings of increased connectivity between the dorsomedial prefrontal cortex and regions within the DMN (Sheline et al., 2010).

Moreover, findings from Mayberg's studies revealed normalization of the increased limbic and paralimbic activations as well as improvement in the initially attenuated dorsal prefrontal activations with successful response to treatment (Mayberg et al., 1999; 2000), suggesting that they may be state factors in depression. However, even individuals who are at high risk for depression have shown greater limbic activations, for instance, in bilateral amygdala, in comparison with low-risk individuals in response to fearful stimuli (Monk et al., 2008). Similarly, remitted MDD patients relative to

controls showed elevated amygdala activity during masked sad facial processing, with a pattern of activations similar to acutely depressed patients (Victor et al., 2010). This suggests that even in vulnerable patients, negative mood induction may mediate amygdala hyperactivity, similar to what is seen in acutely depressed patients.

Apart from analysis of resting state networks, the study of affective cognition is gathering momentum and is considered important in gaining insight into the pathophysiology of mood and anxiety disorders and in understanding the mechanism of antidepressant drug action. Affective cognition, or the response to affective stimuli during cognitive evaluation, involves many sub-processes, which include perception, recognition and in some instances categorization of different emotions (Elliott et al., 2011). Different paradigms have been employed to examine affective cognition, and these include standardized series of facial expressions (ex. Ekman & Friesen, 1976), emotional pictures (ex. International Affective Picture System (IAPS); Lang et al., 1999), memory and attentional bias task with emotional components, and social and moral emotion paradigms (see Elliott et al., 2011 for a selective review). The amygdala plays a key role in emotion recognition, categorization and also emotion memory (Berntson et al., 2007). In addition to amygdalar responses, affective cognition modulates the ventromedial prefrontal region, especially during social and moral emotions, and the connections between the regions; and disruptions in affective cognition are a core feature of depression (Elliott et al., 2011).

Thus, taking into account evidence from resting state studies as well as those that employed different functional paradigms, it seems that depression may be mediated by dysregulation in the cortico-limbic network, as postulated by Mayberg; however different paradigms (whether cognitive, affective or both) or even resting state are likely to probe different components of the same network. Moreover, due to the heterogeneous nature of MDD, there may be distinct neural correlates associated with varying symptomatic profiles, which requires investigation. More recently, multi-network model of psychopathology has provided novel insight into understanding the dysfunctional neural systems in depression (Menon, 2011). This model elucidates three important networks, the DMN, the salience and the central executive networks. Unlike the DMN, the central executive network (CEN) is most

active during cognitive processing, especially during tasks of memory and attention and constitutes regions of the dorslateral prefrontal cortex and posterior parietal regions (Corbetta & Shulman, 2002; Rogers et al., 2004; Sridharan et al., 2008). The salience network (SN) on the other hand plays a key role in emotional processing and emotional control, and comprises the amygdala, insula, dorsal anterior cingulate and the temporal cortex (Mulders et al., 2015). In this network-based model approach, the default mode network, the salience network and the central executive network that characterise neural function during rest, affective and cognitive processing are altered in depression (Menon, 2011). A very recent review of resting state connectivity studies found increased connectivity in the anterior DMN in depression, and between the anterior DMN and the salience network, decreased connectivity between the posterior DMN and the central-executive network, and changed connectivity between the anterior and posterior nodes of the DMN, thus providing support for the notion that depression may be a network-based disorder (Mulders et al., 2015).

In the following paragraphs, I review the effects of treatment, both antidepressant as well as psychotherapies on the functional correlates of depression.

Neuroimaging studies indicate that healthy emotional regulation depends on the interplay between frontal and limbic regions, in particular the amygdala. A frequently applied strategy of emotion regulation involves reinterpreting the meaning of a situation in order to reduce the affective impact, which may be termed cognitive reappraisal (Gross, 2002). The neural correlates of the process of reappraisal involve cognitive control regions within the prefrontal cortex and modulation of emotion-related activity in the amygdala (meta-analysis: Buhle et al., 2014). The amygdala plays a key role in processing of emotional stimuli, both negative and positive, although there is a higher probability of amygdalar response to stimuli which evoke fear and disgust relative to those which give rise to happiness (Costafreda et al., 2008). Studies of the neural correlates of emotional processing in MDD have demonstrated increased amygdala activation during an acute depressive episode as compared to controls in response to a variety of negative stimuli, such as sad faces (Fu et al., 2004; Victor et al., 2010; Arnone et al., 2012), fearful or angry faces (Sheline et al., 2001; Ruhe et al., 2012), and negatively valenced pictures (Anand et al., 2005; Rosenblau et al., 2012).

The effect of treatments on negative affective processing has been studied widely due to the mood congruent processing bias evident in patients with depression. With the current psychiatric drug nomenclature, the different categories are neither based on which neurotransmitters the drugs act on, nor do they reflect the differing mechanism of action of the drug. Such a nomenclature that is centred on earlier understanding of neuropsychopharmacology is less likely to aid clinicians in selecting the best possible treatment course for the patients (Zohar et al., 2014; Ghaemi, 2015). There is a proposal for a new and revised nomenclature from the four major schools of neuropsychology (i.e. the European College of Neuropsychopharmacology, the American College of Neuropsychopharmacology, the Collegium Internationale de Neuropsychopharmacologie, and theAsian College of Neuropsychopharmacology), that is instead based on five exes (1) target or class (primary pharmacological action and mechanism), (2) family (relevant neurotransmitter and mechanism), (3) neurobiological activities, (4) efficacy and side effects, and (5) approved indications (Zohar et al., 2014).

Within the category of antidepressants, there are different classes, and in general, the pharmacological action of antidepressants is enhancing synaptic action of one or more of the monoamines, namely, serotonin, norepinephrine and dopamine, consistent with the monoamine hypothesis of depression. According to this theory, the entire monoaminergic system may be dysregulated in the different neural circuits, and the patients' symptoms vary depending on the involvement of the different monoamine neurotransmitters (Stahl, 2013). The most important antidepressant classes, stratified broadly based on their mechanisms of action include older antidepressants such as are tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAO-I), reuptake inhibitors like serotonin selective reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), selective norepinephrine reuptake inhibitors (NRI), and norepinephrine and dopamine reuptake inhibitors (NDRI), and other antidepressant classes, such tetracyclic antidepressants (TeCA), reversible monoamine oxidase inhibitors (rMAO-A inhibitor) and noradrenergic and specific serotonergic antidepressants (NaSSA), and serotonin antagonist/reuptake inhibitor amongst others (Stahl, 2013; Zohar et al., 2014).

In the paragraphs that ensue, the neural effects of SSRIs on negative emotional processing are discussed in detail as majority of the longitudinal neuroimaging treatment studies in depression have generally examined SSRIs compared to other antidepressant classes. This may at least be partly due to SSRIs being recommended as first line treatment options for MDD patients who are indicated for antidepressant treatment (National Institute for Health and Clinical Excellence; NICE, 2015). Drugs belonging to the SSRI class include fluoxetine, citalopram, escitalopram, sertraline, paroxetine and fluvoxamine. They share a common feature, i.e. selective inhibition of serotonin reuptake or the serotonin transporter (Stahl, 2013). However, each of these drugs also have distinguishing pharmacological features that make it distinctive from the others. The longitudinal imaging studies in depression have examined the neural effects of sertraline (Sheline et al., 2001; Anand et al., 2007; Victor et al., 2010), fluoxetine (Fu et al., 2004), citalopram (Arnone et al., 2012), paroxetine (Ruhe et al., 2012), and escitalopram (Jiang et al., 2012; Rosenblau et al., 2012) on negative emotional processing in depression. Following treatment with SSRIs, normalisation of increased amygdala activation in patients has been widely observed (Sheline et al., 2001; Fu et al., 2004; Arnone et al., 2012; Rosenblau et al., 2012). This may be consistent with the density of serotonin receptors within the amygdala (Xu & Pandey, 2000) which are a target of action for SSRIs (Jiang et al., 2011). Although normalization of amygdala activity in patients could merely reflect improvements in depression severity, recent neuroimaging studies have provided evidence for effects of SSRI treatment on amygdala. For instance, acute administration of citalopram in controls and remitted MDD patients decreased amygdala responses to fearful emotions (Anderson et al., 2011). Furthermore, short term administration of SSRIs in both healthy volunteers (Harmer et al., 2006) and MDD patients (Godlewska et al., 2012) normalized amygdala responses to negative emotional stimuli and remediation of amygdala activity in patients occurred even before clinical improvements (Godlewska et al., 2012), suggesting a therapeutic mechanisms of SSRI treatment for depression. It is important to note that the probability of amygdala activation in response to emotional stimuli is increased using a region of interest (ROI) approach (Sheline et al., 2001; Arnone et al., 2012; Rosenblau et al., 2012), indicating the need for such sensitive methods in addition to whole brain analyses to investigate amygdala activity (Costafreda et al., 2008).

In addition to attenuation of amygdalar activation, antidepressant treatment also normalizes activity in other limbic and subcortical regions that are dysregulated in patients. For instance, MDD patients have shown increased activations in the anterior cingulate, insula (Fu et al., 2004), hippocampus (Victor et al., 2010), parahippocampal gyrus (Surguladze et al., 2005) and putamen (Fu et al., 2004; Surguladze et al., 2005) relative to healthy controls during implicit processing of sad faces which was attenuated with treatment (Anterior cingulate: Fu et al., 2004; Victor et al., 2013; Insula: Fu et al., 2004; Wagner et al., 2010; Putamen: Fu et al., 2004). Limbic regions such as hippocampus, parahippocampal gyrus, orbitofrontal and anterior cingulate cortices are highly responsive to emotional stimuli but are also engaged by other responses that are seen as dysfunctional in depression. For example, orbitofrontal cortex is involved in reward processing (Elliott et al., 2000; Rolls, 2000; Elliott et al., 2003), with greater responses in this region during the lowest and highest reward values relative to mid-values (Elliott et al., 2003), hippocampal gyrus in episodic memory (Burgess et al., 2002) and anterior cingulate in conflict monitoring and cognitive control (Botvinick et al., 2001; Mitterschiffthaler et al., 2008). In response to other affective stimuli, such as negative pictures, antidepressants regulate activity in the prefrontal regions including orbitofrontal and dorsolateral prefrontal cortices (Rosenblau et al., 2012), and subcortical regions including striatum (Anand et al., 2007) which are seen to be highly activated in patients relative to the controls (Anand et al., 2005; Rosenblau et al., 2012). Furthermore, a strong association between cortico-limbic activations and clinical improvements has been observed, such that the patients who showed the most improvement also had the greatest reductions in activation with treatment (Fu et al., 2004).

Investigation of SNRI treatment effects on negative emotional processing in MDD have revealed similar normalization of limbic regions, particularly in the hippocampus, and in other subcortical regions including the fusiform gyrus, thalamus, precuneus and the cerebellum (Frodl et al., 2011) as well as some increases in the insula and anterior cingulate (Davidson et al., 2003) following venlafaxine treatment. SNRI antidepressant drugs, as the name suggests inhibit the reuptake of both serotonin as well as norepinephrine neurotransmitters. A study that examined the effects of duloxetine, another drug belonging to this class, in MDD in response to painful stimuli observed decreases in the insula,

pregenual-subgenual anterior cingulate and the dorsolateral prefrontal regions following treatment (López-Solà et al., 2010). An extended release version of Bupropion, an atypical antidepressant whose mechanism of action is not fully understood, but is known to exert antidepressant effects through modulation of dopaminergic, or noradrenergic systems, or both (Robertson et al., 2007) was also associated with decreased activation in limbic regions, particularly in the amygdala/hippocampal area, anterior cingulate, in the prefrontal regions such as the inferior frontal gyrus and the dorsomedial prefrontal cortex, and in the fusiform gyrus and posterior cingulate cortex in response to negative emotional distractors (Robertson et al., 2007). However, with Mirtazapine, an alpha 2 antagonists, distinct increases have been observed, particularly in the supplementary motor area and middle cingulum during implicit processing of negative facial expressions (Frodl et al., 2011).

The number of studies that have examined the effects of antidepressant drugs belonging to classes other than SSRIs are few, and therefore it is difficult to make accurate comparisons of the common and distinct neural mechanisms of actions of the different antidepressant classes. This is compounded by the observation that there are a lot of variations with respect to the experimental paradigms, sample characteristics, analysis methods and threshold severity, especially amongst studies that examined the effects of drugs belonging to the SNRI class on the functional correlates of depression. For instance, López-Solà & colleagues (2010) administered painful heat stimulation, while Davidson et al. (2003), Schaefer et al. (2006) and Frodl et al. (2011) used classic emotional paradigms such as faces (Frodl et al., 2011) or pictures (Davidson et al., 2003; Schaefer et al., 2006). The study by Robertson & colleagues (2007) used an emotional oddball task, a paradigm that investigated attentional processing and negative emotional processing. In relation to sample characteristics, Schaefer and colleagues (2006) also included patients with primary diagnosis of dysthymia, and with other secondary diagnoses such as generalized anxiety disorder and binge eating disorder. With respect to sample size, all studies except Frodl et al. (2011) had a small patient group of less than 15 participants. The studies also used differing statistical thresholds to examine treatment related effects, with Robertson et al. (2007) particularly utilizing a very lenient threshold ($p < 0.05$, uncorrected) compared to the other studies. None of these studies had a patient group arm receiving placebo, however López-Solà et al. (2010),

Davidson et al. (2003) and Schaefer et al. (2006) at least accounted for effects of time and repeated scans by having healthy controls undergo scans at the same time points as patients.

Due to the lack of well-controlled placebo neuroimaging trials in depression, it is often difficult to separate the neural effects of clinical improvement from that of the drug. However, a meta-analysis in healthy controls based on double-blind placebo controlled trials show some distinct effects of acute antidepressant treatment (Outhred et al., 2013). Acute administration of SSRIs was found to reduce emotional reactivity by normalizing increased activations in the limbic regions, particularly the amygdala, while NRIs increased prefrontal and medial activations, suggesting increased emotion regulation (Outhred et al., 2013). Moreover, amygdala modulation with SSRIs in MDD patients is evident even before patients reported any subjective improvements in clinical symptoms (Godlewska et al., 2012). Similarly, treatment with SNRIs have also shown very early modulation of limbic and prefrtonal regions in MDD patients. For instance, decreases with duloxetine in the insula, hippocampus, anterior cingulate, and additionally in the ventromedial prefrontal regions during painful stimuli (López-Solà et al., 2010) as well as increases with venlafaxine in the insula in response to negative pictures (Davidson et al., 2003) have been observed following one and two week treatment, although both studies also reported significant, albeit modest improvements in depression scores during this time. Furthermore, decreases in the insula and hippocampus (López-Solà et al., 2010) with duloxetine were also previously shown with fluoxetine, but not in placebo responders (Mayberg et al., 2002). In summary, although evidence is not conclusive, there is some preliminary evidence to suggest that SSRI and SNRI classes of antidepressants show similar modulation of limbic hyperactivity, as well as have some distinct effects on brain activity in MDD patients.

1.5 Neural effects of antidepressant treatment during processing of positive emotional stimuli in MDD

Implicit processing of happy facial expressions, on the other hand is associated with decreased activation in MDD patients relative to healthy controls in the amygdala and parahippocampal regions (Lawrence et al., 2004), as well as in the posterior cingulate, precuneus, lingual gyri, and cerebellum, which improved following antidepressant fluoxetine treatment (Fu et al., 2007). Happy facial expressions have also been associated with decreased activations in the fusiform gyrus in MDD patients (Surguladze et al., 2005) which increased following escistalopram treatment (Jiang et al., 2012). The fusiform gyrus is important in face processing (Adolphs, 2002) and it is usually engaged in explicit processing of emotional stimuli. Fusiform responses are greater for attended faces (Pizzagalli et al., 2002), and MDD patients show greater fusiform activation than controls when attending to negative emotional stimuli (versus a neutral baseline) but decreased fusiform responses during attentional processing of positive emotions (meta-analysis: Groenewold et al., 2013). These findings outline the functional network underlying the neurocognitive observations that MDD patients are more likely to attend to faces of increasing sadness in comparison to healthy controls (Gotlib et al., 2004; Joormann & Gotlib, 2007), who in turn attend more to happy facial expressions (Joormann & Gotlib, 2007). Normalisation in fusiform activity following treatment in MDD patients suggest parallels with limbic responses to initially impaired attentional processing of negative as well as positive emotional stimuli.

1.6 Neural effects of antidepressant treatment on cognitive functioning in MDD

Besides the role of antidepressants in normalizing regional brain activations involved in affective processing, they also regulate impaired brain activations associated with more cognitive demands. Tasks of cognitive processing have shown increases in rostral anterior cingulate gyrus (Wagner et al., 2006; Mitterschiffthaler et al., 2008), dorsolateral prefrontal cortex (Wagner et al., 2006), as well as

decreases in the precuneus, cingulate, frontal, occipital regions and brain stem (Kikuchi et al., 2012) in patients relative to controls, during an acute episode. All of these studies (Wagner et al., 2006; Mitterschiffthaler et al., 2008; Kikuchi et al., 2012) had applied variations of the Stroop task to investigate the neural correlates of cognitive control, perhaps as reflected in the variations in their regional responses. Both Kikuchi et al. (2012) and Wagner et al. (2006) modified the Stroop task to include button press response instead of vocalization. Furthermore, Wagner et al. (2006) also presented the response as options along with the target word to reduce memory demand, whilst Mitterschiffthaler et al. (2008) used a variant of the Stroop task that used affective words. Antidepressant treatment was associated with attenuation in the amygdala-hippocampus, prefrontal, and parietal regions in MDD patients (Wagner et al., 2010), providing further evidence that antidepressants modulate cortico-limbic activations that are impaired in depression.

1.7 Antidepressant treatment effects on neural connectivity in MDD

It has been theorised that depression results from abnormal connections between the limbic regions, such as the amygdala, and other parts of the brain. Therefore, in order to examine the relationship between regions which may be excessively engaged, impaired or unaltered in depression, a connectivity analysis attempts to define the interaction between brain regions. The amygdala has connections with the subgenual anterior cingulate cortex (ACC) and receives connections from dorsal cingulate cortex (Aggleton & Saunders, 2000). Reduced frontocortical and limbic regional connectivity has been observed in MDD (Anand et al., 2005; Chen et al., 2008; Costafreda et al., 2013) which may worsen with increasing severity of depression (Matthews et al., 2008; Friedel et al., 2009). Moreover, non-responders to antidepressants can be differentiated from responders based on their pre-treatment functional connectivity (Lisiecka et al., 2011). The use of multimodal neuroimaging techniques, for instance, fMRI and PET in combination have rendered further support for dysfunctional connectivity between the limbic and frontocortical region in MDD patients during processing of emotional stimuli (Irwin et al., 2004). The reduced frontocortical and limbic coupling

observed in acutely depressed patients tend to improve following successful antidepressant treatment (Chen et al., 2008).

Interestingly, lateralization effect of antidepressants have been observed, such that the effect on amygdala coupling was predominant for the left amygdala compared to the right (Chen et al., 2008). Activation of the lateral prefrontal and dorsal cingulate cortices suppresses amygdala activation, part of the process of voluntary emotional down-regulation (Costafreda et al., 2008). These findings indicate that depression is associated with impairments in the inhibitory influence of cortical regions on limbic regions, which may improve with treatment.

1.8 Neural effects of psychological therapy

Fewer studies to date have investigated the neural correlates of psychological therapy. Increases in baseline activations in the amygdala-hippocampal regions in MDD patients relative to healthy controls have been followed by significant reductions following treatment with short term cognitive behavioural therapy (CBT) (Fu et al., 2008a) as well as with long term psychodynamic psychotherapy (Buchheim et al., 2012). Increases within the prefrontal regions in MDD patients, such as the medial prefrontal (Buchheim et al., 2012; Yoshimura et al., 2014) and orbitofrontal (Dichter et al., 2010) cortex are also normalized following a variety of forms of psychological treatments, including CBT (Yoshimura et al., 2014), behavioural activation therapy (Dichter et al., 2010) and psychodynamic psychotherapy (Buchheim et al., 2012). In the anterior cingulate, several studies have demonstrated increased activation (Fu et al., 2008a; Dichter et al., 2009) but there have also been reports of decreases (Buchheim et al., 2012) in activation following psychological therapy. There is a growing evidence to suggest that the medial prefrontal cortex plays an important role in self-referential processing of negative stimuli (Kelley et al., 2002), which is common in rumination and depression (Nolen-Hoeksema et al., 2008). It has been proposed that treatment with psychotherapy significantly impacts on the brain regions involved in emotion processing disturbances in MDD patients. The

studies though have been limited to date along with variations with respect to treatment, treatment duration, and task processing which require further study.

The differential effects of pharmacological and psychological therapies on regional brain activity have been investigated using resting state positron emission tomography (PET) (Brody et al., 2001; Goldapple et al., 2004; Kennedy et al., 2007) and single-photon emission computed tomography (SPECT) (Martin et al., 2001). These studies have generally compared cognitive behavioural therapy (Goldapple et al., 2004; Kennedy et al., 2007) or interpersonal psychotherapy (Brody et al., 2001; Martin et al., 2001) with antidepressant drugs such as paroxetine (Brody et al., 2001; Goldapple et al., 2004) or venlafaxine (Martin et al., 2001; Kennedy et al., 2007). MDD patients in an acute episode were assigned randomly to either psychological therapy or pharmacological intervention (Martin et al., 2001; Kennedy et al., 2007), although few studies have used a nonrandomized design, in which treatment type was guided by patient preference (Martin et al., 2001) or CBT treatment group were compared post-hoc to an independent group of paroxetine responders (Goldapple et al., 2004). Both antidepressant treatment and psychotherapy were associated with reductions in the prefrontal cortex, including the middle frontal gyrus (Brody et al., 2001), lateral orbital, dorsomedial (Kennedy et al., 2007) and ventral (Goldapple et al., 2004) prefrontal cortex, as well as increases in the basal ganglia (Martin et al., 2001) and the temporal lobe (Brody et al., 2001). Antidepressants were specifically associated with decreases in the limbic regions such as the insula (Goldapple et al., 2004), posterior (Kennedy et al., 2007) and ventral (Goldapple et al., 2004) subgenual cingulate regions. In addition, widespread increases in the posterior temporal lobe (Martin et al., 2001), brainstem and the cerebellum (Goldapple et al., 2004) were also observed. Psychological therapies, on the other hand were associated with decreases in the thalamus (Kennedy et al., 2007), orbitofrontal, medial and ventrolateral prefrontal cortices (Goldapple et al., 2004), as well as increases in the subgenual (Kennedy et al., 2007) and dorsal (Goldapple et al., 2004) cingulate regions. In the posterior cingulate region, however, some inconsistencies have been noted with reports of both decreases (Goldapple et al., 2004) as well as increases (Martin et al., 2001) in activations with psychological therapy.

It has been proposed that cognitive therapy shows a cortical "top-down" mechanism of action, as it focuses on altering memory and attention processes that are involved in the mediation of cognitive biases and maladaptive processing of information (DeRubeis et al., 2008). Antidepressants, may also show a similar mechanism of action to cognitive therapy whereby antidepressant modulate the negative biases and memory impairments in depression very early on in the course of treatment, even before patients report any change in their mood or anxiety (Harmer et al., 2009a, 2009b). The common neural mechanisms of action of antidepressants and cognitive therapy may reflect their targeting similar underlying processes that lead to improvements in depressive symptoms.

1.9 Functional neuroimaging predictors of clinical response

In addition to examining treatment effects in major depression, identifying biomarkers of responses to treatment is crucial as it could lead to the development of novel strategies to augment existing treatment methods. Meta-analysis of pharmacological and psychotherapeutic treatment studies showed that increased baseline activity in the anterior cingulate, medial prefrontal and orbitofrontal regions was predictive of a better response to treatment, whilst activity in the right striatum and anterior insula was predictive of a poorer prognosis (Fu et al., 2013). Specific sub-regions of the anterior cingulate cortex, namely the pregenual and the subgenual ACC are important targets for antidepressant action, and could be good predictors of clinical response (Chen et al., 2007).

Increased anterior cingulate activity as being predictive of response to antidepressant medications, prior to the initiation of treatment, has been highly replicated, while the evidence for CBT has been more mixed (Fu et al., 2013). The predictive function of the anterior cingulate has been observed with numerous tasks, including resting state PET studies (Mayberg et al., 1997; Kennedy et al., 2007) and with both cognitive (Marquand et al., 2008; Roy et al., 2010) and emotional processing (Davidson et al., 2003; Chen et al., 2007; Costafreda et al., 2009a; Keedwell et al., 2010) MRI tasks. However, findings of potential biomarkers from these studies were obtained from group comparisons; and in order for a biomarker to have a clinical impact, it is important that the measure is able to provide a

classification with high level of accuracy for an individual (Fu et al., 2008b). Moreover, there have also been some inconsistencies in results as some studies showed that greater anterior cingulate activity was predictive of a poorer clinical response to pharmacotherapy (Brody et al., 1999; Konarski et al., 2009) as well as to CBT (Siegle et al., 2006; Konarski et al., 2009). Elicitation of anterior cingulate in response prediction is usually seen in response to negative emotional stimuli (Davidson et al., 2003; Chen et al., 2007; Keedwell et al., 2010) rather than towards positive ones. The anterior cingulate plays a key role in emotion processing, and specific sub-regions, namely the pregenual and subgenual anterior cingulate can be good predictors of clinical response as they are important targets of antidepressant action (Chen et al., 2007). There is evidence that the anterior cingulate is more likely to get activated during tasks of cognitive demand (Duncan & Owen, 2000) and therefore it may be a more reliable functional marker of treatment response during specific task processing rather than during resting state. The insula is engaged by negative emotional stimuli (Anand et al., 2005; Van Dillen et al., 2009) in particular the anterior region for social stimuli, with interoceptive integration of internal and external stimuli of emotional pain recognition (Singer et al., 2004). More recently, hypometabolic activity in the insula was associated with remission to CBT and poor response to escitalopram, whilst the opposite effect was seen with insula hypermetabolism, suggesting that pre-treatment metabolic activity in the insula can be used to inform initial choice of treatment in depression (McGrath et al., 2013).

1.10 Neuroimaging biomarkers of diagnosis and treatment response

At the present time, the diagnosis of depression is based solely on clinical signs and symptoms, and there are no biological tests that are used to diagnose the disorder or to predict clinical response. Methods of analysis based on machine learning algorithms, such as Support Vector Machines (SVM) have been applied to neuroimaging measures to predict diagnosis, course of illness and treatment prognosis as they facilitate individual level classification (Nouretdinov et al., 2011; review: Wise et al., 2014). SVM uses a classification algorithm that allows categorization of unseen individual data

into specific groups (for instance, either patients or controls) based on a training data set (Orrù et al., 2012). Such biomarkers can be identified with high predictive accuracy at the individual level even before the initiation of treatment or very early on during the course of treatment. For instance, baseline neural activity during sad facial processing predicted remission to CBT with a sensitivity of 71 % and a specificity of 86% (Costafreda et al., 2009a), while remission to antidepressants showed a trend towards significance (Fu et al., 2008b). Evidence from structural data, on the other hand revealed that grey matter density predicted clinical response to antidepressant, in particular in the anterior cingulate (Costafreda et al., 2009b; Nouretdinov et al., 2011). For diagnostic prediction, the pattern of baseline neural activity during sad facial expression accurately classified 84% of the patients and 89% of controls (Fu et al., 2008b), while neural correlates of verbal working memory showed reduced accuracy (Marquand et al., 2008). Further investigations of neuroimaging as well as other biological measures are required to develop clinically useful biomarkers of clinical response. Future research should also aim to investigate whether integration of neuroimaging biomarkers based on multiple neural processes associated with depression (ex. affective and emotional processing and structural neuroimaging) would achieve more accurate classification. This would be of particular benefit to patients whose may be less likely to improve solely with conventional treatment methods and would benefit from an earlier initiation of alternative or combination therapies.

1.11 Conclusions

In summary, research has begun to elucidate the function of antidepressants and psychotherapy in modulating the regions involved in the emotional, cognitive and behavioural disturbances that underlie major depression. Limited number of PET studies have examined the functional correlates of placebo effect in depression (ex. Mayberg et al., 1999, 2000) and none of the fMRI studies, to my knowledge, had included a patient group receiving a placebo treatment. Future placebo-controlled longitudinal fMRI studies would assist in distinguishing between the effects of treatment and changes associated with depressive state and to control for effects of time and test-retest with particular

neuroimaging paradigms. Additional investigations are also required to determine the common and distinct mechanisms of action of antidepressants and psychological therapies. Pattern classification based analysis of neuroimaging data is beginning to delineate potential biomarkers for both diagnosis and prognosis with high predictive accuracy at the individual level which will aid in the development of clinically useful measures.

1.12 Aims and Objectives

The main objective of this thesis is to examine the neuropsychological abnormalities associated with emotional and cognitive processing and how they change with treatment. These processes were especially chosen, since there is a sizeable body of evidence associating affective biases and cognitive impairments to the aetiology and maintenance of depression, as detailed in this chapter. Owing to the scarcity in the literature in longitudinal studies examining treatment strategies other than SSRIs, it is unclear whether the regional changes seen after treatment is specific to a class of pharmacotherapy; or whether such changes are common across different classes of antidepressant drugs and even across different treatment modalities. Three chapters in this work attempt to bridge this gap in the literature. In Chapter 2, the neural correlates of Cognitive Behavioural Therapy (CBT) on dysfunctional attitudes are examined. A paradigm termed the 'modified dysfunctional attitude scale' (mDAS; Sankar et al., 2014) was developed to examine negative thinking, a common feature associated with depression. The neural effects of CBT are especially examined as one of the aims of CBT is to address dysfunctional attitudes which contribute to the persistence of depressive symptoms (Dobson & Dozois, 2001).

The effects of a dual acting SNRI, duloxetine, on affective and cognitive impairments in depression are investigated here in two separate branches of their own (Chapters 3 & 4). First, affective biases were studied using a series of sad and happy facial expressions adapted from the standardized Ekman and Freisen's Pictures of Facial affect (Ekman & Friesen, 1976). Secondly, a modified Sternberg task

was used to examine cognitive biases, specifically impairments in working memory, in patients with depression.

In order for neuroimaging findings to have tangible clinical applications, it is important that we are able to develop biomarkers that can predict therapeutic response in MDD with high accuracy at the individual level. Therefore, another key focus in the thesis is to examine the potential of structural neuroimaging data to identify depression and predict clinical outcome using machine learning algorithms (Chapter 5). This is significant as it helps optimize treatment strategies at an early stage. In particular, this means we can provide alternate treatment options early on for those who are less likely to benefit from conventional methods.

1.13 Hypothesis

Explicit hypotheses and background literature are detailed in the individual chapters contained herein. Overall, it is hypothesised that MDD patients would show increased activations in the limbic regions, especially in the amygdala during processing of negative emotional stimuli, such as sad facial expressions and negative dysfunctional attitudes, which would attenuate with duloxetine and CBT respectively. It is also expected that during the Sternberg paradigm, MDD patients would show increased activations in regions associated with working memory, such as the inferior frontal and the dorsolateral prefrontal regions, in comparison with controls, which would normalise with duloxetine treatment.

In the examination of biomarkers of diagnosis, it is hypothesised that the structural correlates of prefrontal, parietal and temporo-occipital regions would show significant predictive power for MDD diagnosis. For prognostic markers, in line with the literature, it is expected that the anterior cingulate would show high predictive accuracy for clinical outcome at the level of the individual.

2 Neural effects of cognitive behavioural therapy on dysfunctional attitudes in major depressive disorder

The important findings from the chapter are included in the paper listed below:

Sankar, A., Scott, J., Paszkiewicz, A., Giampietro, V., Steiner, H., & Fu, C. (2014). Neural Effects of Cognitive–Behavioural Therapy on Dysfunctional Attitudes in Depression. *Psychological Medicine*, 1-9.

The preliminary neuroimaging analyses presented in this chapter were performed as part of my MSc project titled "Dysfunctional thinking in major depressive disorder: Neural mapping and analysis following cognitive behavioural therapy". However, more complex second level analyses for the contrast DAS-cDAS, including examining main effect of group at baseline, main effect of group at week 16 for extreme attributions, main effect of group at baseline, main effects of group at week 16 for regular attributions, main effect of task (DAS< cDAS & cDAS>DAS) for baseline, and then again at week 16, correlation between baseline activations and improvements in depression scores, correlations of change in baseline activations with reduction in HAMD scores; preparation of the manuscript for publication, revisions and re-submissions were done during my PhD studies. This chapter has been added to the PhD thesis due to its relevance to the thesis topic and the volume of work carried out during my PhD.

2.1 Introduction

Beck (1967) postulated that negative life incidents, especially those very early on in life can lead to the development of negative "schemas" which involve themes of loss, failure and abandonment. Dysfunctional attitudes, such as "If I fail partly, it is as good as being a complete failure", are activated during stressful life events and are characteristic of a depressive episode (Haaga et al., 1991). Negative or dysfunctional patterns of thinking are typically measured using the Dysfunctional Attitude Scale (DAS) (Weissman & Beck, 1978), which is a self-report inventory in which individuals indicate the extent to which they agree or disagree with a series of functional and dysfunctional attitude statements. It has been proposed that depressive symptoms are promoted by dysfunctional attitudes (Sheppard & Teasdale, 2000). According to the circular causality hypothesis, dysfunctional attitudes and negative emotions have a reciprocal causal effect (Burns & Spangler, 2001). In support, positive associations between depression severity and dysfunctional attitudes have been observed (Beevers et al., 2003), which revert to normal during remission (Haaga et al., 1991), and the magnitude of dysfunctional thinking during a dysphoric mood state is predictive of a subsequent depressive relapse (Segal et al., 2006).

High levels of dysfunctional thinking during a depressive episode have been associated with greater $5HT_2$ receptor binding potential in the anterior cingulate, prefrontal regions, thalamus, caudate and putamen (Meyer et al., 2004). Administration of the serotonin agonist d-fenfluramine led to a reduction in dysfunctional attitudes, suggesting that serotonin agonism can reduce dysfunctional attitudes by inducing neuronal release of serotonin in depression (Meyer et al., 2003). Although a correlation with receptor binding potential and negative attributions has been observed, subjects were not actively engaged in a dysfunctional attitudes task during the brain scan. In the present fMRI study, the DAS task was administered whilst patients were in the scanner to provide a more accurate measure of regional brain activations associated with dysfunctional thinking.

An aim of CBT is to address dysfunctional attitudes which contribute to the persistence of depressive symptoms (Dobson & Dozois, 2001). Functional imaging studies of patients with major depressive

disorder during an acute episode and following treatment with CBT have revealed modulation of amygdala and anterior cingulate activity with therapy. For instance, amygdala hyperactivity to negative emotional stimuli in depressed patients has been widely reported (Fu et al., 2004, Surguladze et al., 2005, Fu et al., 2008a) with some evidence of normalization following CBT (Fu et al., 2008a). Furthermore, following treatment with CBT, increased activity has been observed in the anterior cingulate during a resting state (Goldapple et al., 2004), in response to sad faces (Fu et al., 2008a), and with self-referential processing to positive stimuli though not to negative stimuli (Yoshimura et al., 2014). The role of anterior cingulate as a predictor of treatment response has been consistently observed (meta-analysis: Fu et al., 2013). Additional neural correlates of CBT in depression include increases in ventromedial cortical activity (Ritchey et al., 2011), decreases in dorsal frontal cortical activity (Kennedy et al., 2007), and increases in hippocampal activity during a resting state (Goldapple et al., 2004). The changes in prefrontal, limbic and subcortical activity are generally consistent with models of neurocognitive circuits in depression and the effects of CBT (DeRubeis et al., 2008).

However, the brain regions engaged by dysfunctional thinking in depression and the effects of CBT have not been examined. The present study sought to investigate the neural correlates of dysfunctional attitudes in patients with depression during an acute depressive episode and following treatment with CBT. It is hypothesised that patients would show greater endorsement of dysfunctional attitudes during an acute depressive episode, which would improve following treatment with CBT. It is also hypothesized that MDD patients would show greater activation in the anterior cingulate and other regions associated with attention and self-referential processing with extreme attributions relative to healthy controls. It is also expected that regions associated with attentional processing of negative stimuli would show increased activity in patients during an acute depressive episode which would resolve following CBT. In particular, it is hypothesised that patients would show increased amygdala activity which would normalise following CBT.

2.2 Methods

2.2.1 Participants

Depressed Group: Sixteen participants (13 women, age 40.00, [SD 9.27]) who met criteria for MDD by Structured Clinical Interview for DSM-IV (SCID) (Fu et al., 2008a) and a clinical interview with a psychiatrist were recruited through local newspaper advertisements.

The inclusion criteria were an acute episode of major depressive disorder, unipolar subtype and a score of at least 18 on the 17- item Hamilton Rating Scale for Depression (HRSD) (Fu et al., 2008a). The exclusion criteria were a current neurological disorder, history of neurological trauma resulting in a loss of consciousness, history of diabetes or medical disorder, other Axis I disorders including anxiety disorder or history of substance abuse within 2 months of participation in the study. All patients were free of psychotropic medications for a minimum of 4 weeks at the time of recruitment (8 weeks for fluoxetine) and remained medication free throughout the treatment.

Control Group: Sixteen age, gender and IQ matched healthy controls with HSRD scores less than 8 (13 women, age 39.94 years [SD= 9.48]) and no history of previous psychiatric illness, neurological disorder or head injury resulting in a loss of consciousness were recruited through local newspaper advertisements.

All participants provided written, informed consent. The study was approved by the Institute of Psychiatry and South London and Maudsley (SLaM) NHS Ethics Research Committee. The HRSD (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck, 1961) were measured at baseline and following the course of CBT at the end of 16 weeks.

2.2.2 Dysfunctional attitude scale (DAS)

The DAS measures pervasive negative attitudes towards the self, the world and the future. The widely used DAS consists of 66 statements reflecting dysfunctional attitudes (“I should be upset if I make a mistake”) and 34 statements reflecting functional attitudes (“I do not need the approval of other people in order to be happy”). Participants respond to each statements using a 7 point Likert

scale, ranging from totally agree to totally disagree (reverse scoring is applied to functional statements such that the highest score on any item represents the most dysfunctional response); the maximum score is 700.

In the present study, the DAS 24 (Power et al., 1994) was used, which is a shortened version of the DAS (Weissman & Beck 1978) consisting of 24 statements. 24 neutral statements were included as a control task for the present study, which the authors of the study called the control DAS (cDAS). The resulting 48 item scale was termed as the 'modified Dysfunctional Attitude Scale' (mDAS -48). During the fMRI scan, participants were presented with the mDAS-48 task consisting of statements alternating from the DAS and cDAS. There were a total of 48 statements (24 cDAS and 24 DAS statements). After 6 statements of alternating DAS and control DAS statements, a thirty second rest period was given to each subject before proceeding with the next set of six statements. Total duration of the task was 1645 seconds.

Subjects were asked to respond to each statement using a 7 point Likert scale, ranging from totally agree to totally disagree. Extreme responses are a reflection of the endorsement of dysfunctional attitudes (Power et al., 1994). The fMRI task began with either a DAS or cDAS statement which was presented in a counterbalanced order for consecutive participants, and the same version was used for the same participant. fMRI scans were acquired at baseline (week 0) and upon study completion (week 16). Each MRI scan was up to 1.5 hours in duration consisting of fMRI tasks and structural MRI scans, and data from an affective facial processing task have been published in Fu et al. (2008a).

All behavioural data were recorded during the fMRI scans and analysed using SPSS (Version: PASW Statistics 18). Repeated measures ANOVA was used to analyse main effect of group (patients *vs* controls), main effect of statement (DAS *vs* cDAS), main effect of time (week 0 *vs* week 16) and group by time interactions (i.e. changes in response between baseline and final trials). Percentage change in extreme attributions (total number of extreme DAS scores at week 16 – total number of extreme DAS scores at baseline / total number of extreme DAS scores at baseline * 100) was also calculated for each subject.

2.2.3 CBT treatment

Patients received 16 sessions of CBT with experienced therapists (Fu et al., 2008a). The standard CBT procedures as described by Beck et al. (1979) were followed, and all therapists met the required level of training and proficiency (Paykel et al., 1999). The CBT sessions were audiotaped and reviewed to ensure adherence and competence. HRSD scores were obtained from patients at baseline and after 16 weeks of CBT. Treatment response was defined as a minimum reduction of 50% in HRSD score from baseline.

fMRI image acquisition

Gradient echo echoplanar Imaging (EPI) data were acquired on a GE Sigma 1.5 T system (General Electric, Milwaukee, USA), at the Maudsley Hospital, London. A total of 441 T_2 – weighted images depicting blood – oxygen- level – dependent (BOLD) contrast were acquired over 27 minutes (for each run) at each of 22 near- axial noncontigious 3 mm planes parallel to the inter commissural (AC PC) line: time to echo (TE) = 40 msec, repetition time TR =3.74 secs, in - plane resolution = (3.75) mm, interslice gap 0.3 mm and matrix size 64 x 64 voxels. This EPI dataset provided almost complete brain coverage. Four dummy acquisitions were made at the beginning of each scan to allow magnetization to reach equilibrium amplitude.

2.2.4 fMRI data analysis

2.2.4.1 Individual analysis

Images were first realigned to minimise subject head motion (Bullmore et al., 1999) and then smoothed using a Gaussian filter (full width at half maximum = 7.2 mm). Responses to the experimental paradigm were detected by carrying out time series analysis using two gamma variate functions (peak responses at 4s and 8s respectively) to model the BOLD response. The best fit between the weighted sum of these functions (convolved with each component of the experimental design) and the time series at each voxel was computed using the constrained BOLD effect model developed by Friman et al. (2003). Following this, a goodness of fit statistic was computed at each

voxel, and for each experimental condition. This consisted of the ratio of the sum of squares of deviations from the mean image intensity due to the model (over the whole time series) to the sum of squares of deviations due to the residuals, termed the SSQ ratio. The data were then permuted using a wavelet-based method calculating the null distribution of SSQ ratios under the assumption of no experimentally determined response (Bullmore et al., 2003). This distribution can then be used to compute critical SSQ ratio values and then find the associated statistical threshold yielding less than one Type I error voxel/cluster per map. The detection of activated regions was extended from voxel to cluster level (Bullmore et al., 2003). In order to minimise the potential confounding effects of between-group and between-condition variation in task performance, the analysis of the BOLD response data of each subject was modelled using trials associated with correct responses only. In addition to the SSQ ratio, the percentage BOLD change at each voxel was also calculated from the model fit.

2.2.4.2 Group analysis

The SSQ ratio data for each individual were transformed into the standard space of Talairach and Tournoux (Talairach & Tournoux, 1988), using a two stage warping procedure. Group activation maps were then computed contrasting the median SSQ ratio at each voxel in the observed and permuted maps (Brammer et al., 1997). Permutation methods and median statistics were used to obtain the null distribution of SSQ ratios, and the statistical thresholds were set in such a way as to obtain less than one Type I error 3D cluster per brain. For the present group analysis, less than 1 false positive clusters were expected at $p < 0.05$ for voxel level and $p < 0.01$ at cluster level. Only those voxels at which all subjects contributed data were included for analysis (Fu et al., 2008a).

In order to examine the neural correlates of dysfunctional attributions, the fMRI time series corresponding to attributions which corresponded to endorsements of 1, 2, 6, or 7 on the Likert scale were encoded. The fMRI time series associated with regular attributions were encoded by Likert scale responses of 3, 4 or 5. A 2 X 2 ANOVA was employed to examine the main effect of group (patients *vs* healthy controls across both time points), main effect of time (week 0 *vs* week 16) and the group by time interaction. The analyses were examined for regular attributions made to DAS relative

to control DAS statements. For the extreme attributions, predictors of clinical response were examined by correlating baseline activity with change in HAMD scores. Additionally, correlation between change in BOLD response and reduction in HAMD scores were also performed.

2.3 Results

2.3.1 Demographic results

There were no significant group differences in mean age, full IQ, verbal IQ and performance IQ (all $p > 0.05$) (Table 2.1). All patients completed a full course of 16 weeks CBT. There was an expected significant difference in HRSD scores between the groups at week 0 ($F_{1, 30} = 1765.21$, $p < 0.001$) and at week 16 ($F_{1, 30} = 18.96$, $p < 0.001$). Patients showed a significant reduction in mean HRSD scores from baseline to week 16 ($F_{1, 15} = 118.45$, $p < 0.001$).

Table 2.1: Demographic and clinical characteristics

	Healthy Controls	**MDD Patients**
Number of participants	16	16
Male/Female	3/13	3/13
Age	40.00 (9.27)	39.94 (9.48)
Full IQ	123.44 (10.63)	120.03 (14.02)
Verbal IQ	120.44 (11.98)	118.09 (15.95)
Performance IQ	122.31 (11.74)	118.34 (13.37)
Age of onset	NA	33.8 years (range: 18-53 years)
Number of previous episodes	NA	0.63 (range: 0-2)
Duration of current episode	NA	1.64 years (range: 0.2-4 years)
Number of treatment trials for present episode	NA	0.13 (range: 0-1 trials)
HRSD scores at baseline	0.19 (0.05)	20.88 (1.89)
HRSD scores at week 16	0.56 (1.15)	6.37 (5.21)

Mean values are presented with standard deviations in parenthesis, unless otherwise specified.

2.3.2 Behavioural data

The extreme responses to the DAS statements showed a significant group by time interaction effect ($F_{1, 30}$ = 7.434, p = 0.011), in which patients showed a significant reduction in mean number of extreme responses following a course of CBT (t = 2.938, df = 15, p = 0.010), while healthy controls did not have a change in extreme scores at the follow up scan as compared to baseline (t = -0.659, df = 15, p = 0.520) (Table 2.2). There was also a trend towards a significant effect of time ($F_{1, 30}$ = 3.681, p = 0.065) as participants showed a reduction in extreme responses at the follow up scan. There was no significant main effect of group in extreme responses ($F_{1, 30}$ = 0.016, p = 0.900) (Table 2.2, Supplementary material 1a).

In the control DAS statements, there were no significant main effects of time ($F_{1, 30}$ = 2.054, p = 0.162), group ($F_{1, 30}$ = 0.140, p = 0.711), or group by time interaction effects ($F_{1, 30}$ = 3.343, p = 0.077) (Supplementary material 2a).

There were no significant correlations between the change in HRSD scores and the change in the number of extreme responses made to the DAS statements in MDD patients (r = 0.465, $p > 0.05$, 1-tailed test). I was also interested in examining the relationship between changes in DAS scores and response to treatment (a minimum reduction of 50% in HRSD score from baseline). However, the number of patients who did not respond to treatment (n = 3) was insufficient to compare with those who responded (n = 13). Hence, I report the mean percentage change in extreme DAS scores in responders (mean: 13.34, SD: 33.66) and non- responders (mean: 12.8, SD: 15.75).

Table 2.2: Behavioural performance on DAS task

	Healthy Controls	MDD Patients
DAS task		
Week 0		
Extreme attributions	13.94 (4.11)	15.82 (5.45)
Regular attributions	10.06 (4.10)	8.18 (5.62)
Week 16		
Extreme attributions	14.44 (3.67)	12.94 (4.46)
Regular attributions	9.56 (3.67)	11.06 (4.46)
Control DAS task		
Week 0		
Extreme attributions	13.88 (4.44)	15.88 (3.84)
Regular attributions	10.12 (4.44)	8.12 (3.61)
Week 16		
Extreme attributions	14.12 (3.91)	13.43 (3.85)
Regular attributions	9.88 (3.91)	10.57 (3.85)

Mean values are presented and standard deviations in parenthesis

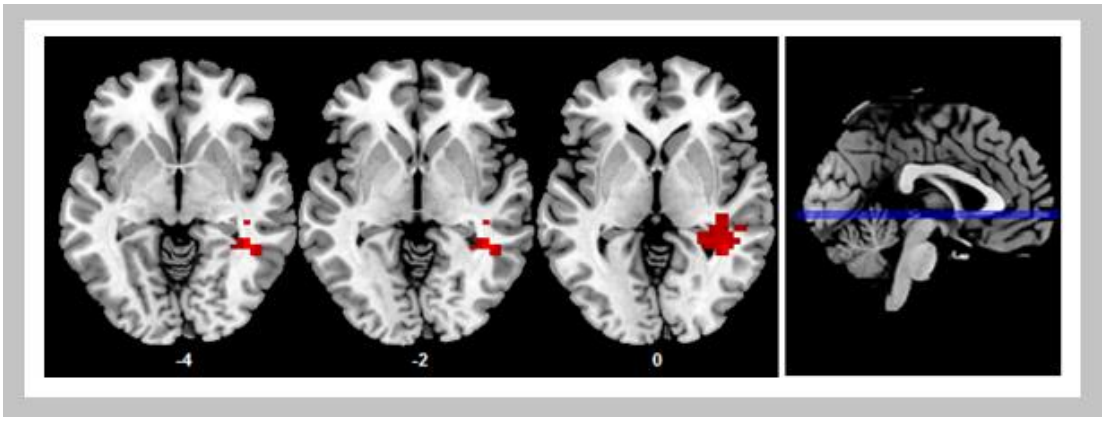
2.3.3 fMRI results

2.3.3.1 Neural responses to extreme attributions in DAS

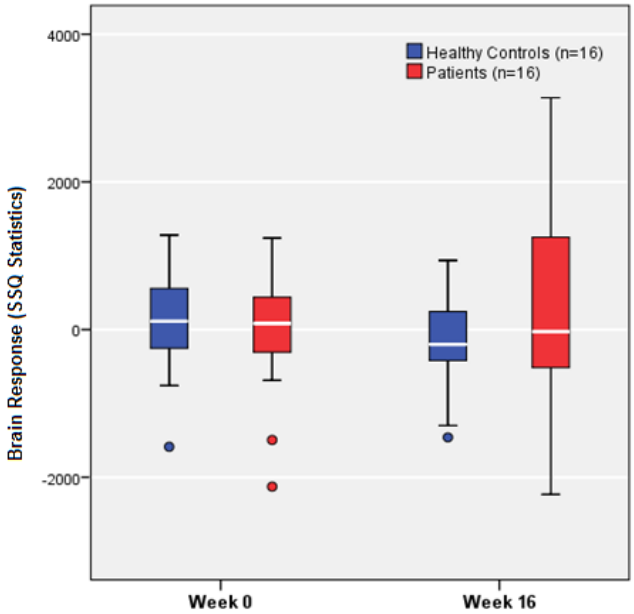
2.3.3.1.1 Group by time interaction effect

A significant group by time interaction effect for extreme attributions to DAS statements was found in the left parahippocampal gyrus (BA 37) (Talairach coordinates: x, y, z = -36, -41, -7; cluster size = 41 voxels, corrected p = 0.0027). The parahippocampal gyrus showed less attenuated activation in MDD patients as compared to healthy controls at week 16 (Figure 2.1).

Figure 2.1: Group by time interactions in the left parahippocampal gyrus



(a) There was a significant group by time interaction effect in the left parahippocampal region for extreme attributions to DAS statements (corrected p = 0.0027). Both depressed patients and healthy controls showed a decrease in activation in the left parahippocampal gyrus at the follow up scans but to a lesser extent in patients. Transverse sections of the brain are presented with the Talairach z-coordinates indicated.



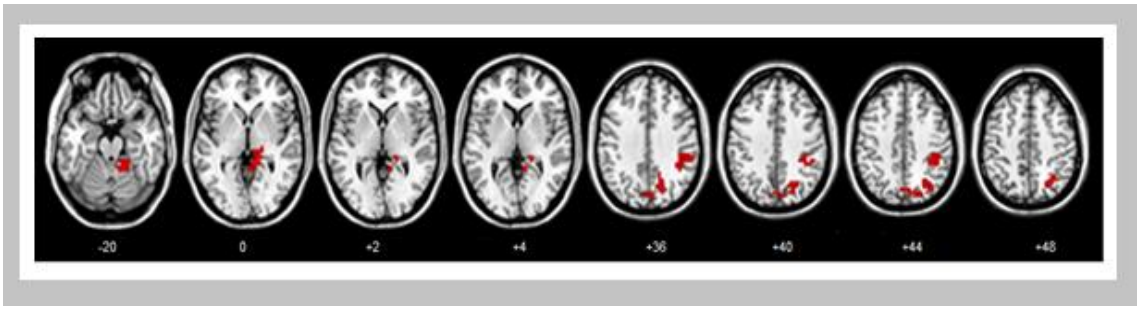
(b) The graph presents the group by time interaction effect in the left parahippocampal region. The boxes indicate interquartile range. The horizontal lines in the boxes represent medians. The limit lines indicate ranges excluding outliers, and the circles represent outliers which are defined as points greater than 1.5 times the interquartile range from the limits of the interquartile range. The y-axis SSQ (sum of squares) values represent normalised statistic of the brain response.

2.3.3.1.2 Main effect of group

There was a significant main effect of group in which patients showed greater activation in the left hippocampal region (coordinates: x, y, z = -11, -33, -3; cluster size = 27 voxels, corrected p = 0.0016), left inferior parietal lobe (BA40) (coordinates: x, y, z = -36, -33, 40; cluster size = 55 voxels,

corrected p = 0.0013) and left precuneus (BA 7) (coordinates: x, y, z = -14, -67, 33; cluster size = 109 voxels, corrected p = 0.00006) relative to healthy controls. The left cerebellum, on the other hand showed greater activation in healthy controls as compared to MDD patients (coordinates: x, y, z = -11, -44, -23; cluster size = 45 voxels, corrected p = 0.0016) (Figure 2.2).

Figure 2.2: Main effect of group



In the main effect of group, MDD patients showed significantly greater activation in the left hippocampus (corrected p = 0.0016), left inferior parietal lobe (corrected p = 0.0013) and left precuneus (corrected p = 0.0006), relative to healthy controls. Healthy controls showed a greater activation in left cerebellum (corrected p = 0.0016) compared to depressed patients. Transverse sections of the brain are presented with the Talairach z-coordinates indicated.

2.3.3.1.3 Main effect of time in MDD patients

In patients, the right posterior cingulate gyrus (BA 30) (coordinates x, y, z = 11, -44, 23; cluster size = 73 voxels, corrected p = 0.006) (Talairach coordinates x, y, z = 11, -44, 23; cluster size = 73 voxels, corrected p = 0.006) showed decreased activation from week 0 to week 16, while no regions showed greater activation at week 16 relative to week 0.

2.3.3.1.4 Main effect of time in healthy volunteers

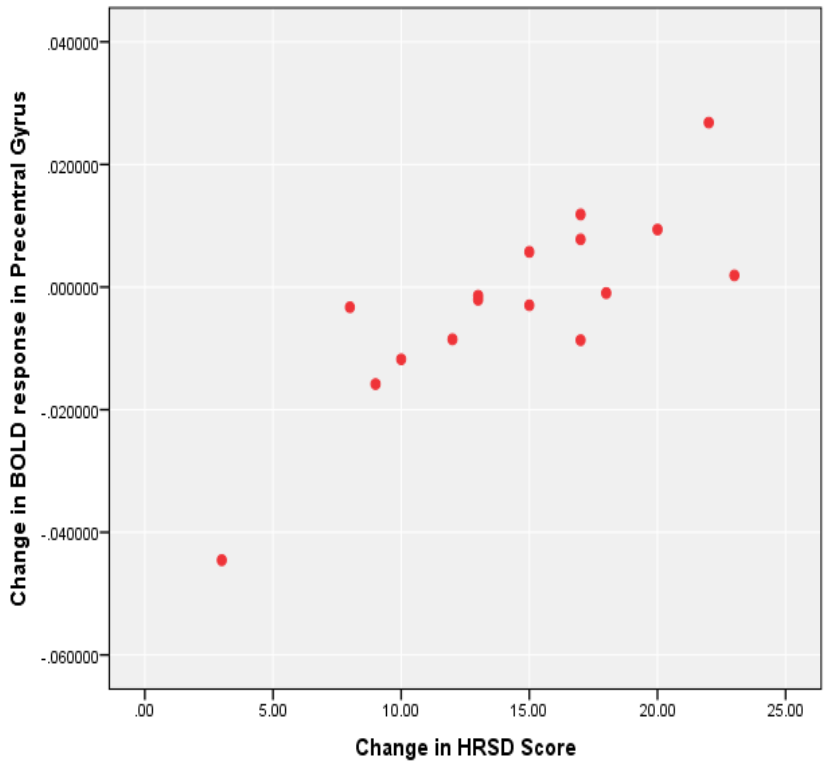
In healthy controls, no regions showed decreased activation from week 0 to week 16, but there was a significant main effect of time in the left cuneus (BA 18) (coordinates x, y, z = -18, -78, 17; cluster size = 53 voxels, corrected p = 0.005) which showed increased activation from the initial to the final scan.

2.3.3.1.5 Correlation with change in HRSD score

Patients showed a significant positive relationship between changes in HRSD score and overall activity in the left precentral gyrus (BA 6) (coordinates x, y, z = -43, -4, 40; cluster size = 28 voxels, r

= 0.739, corrected p = 0.004), in which patients with the greatest improvement in HRSD scores following CBT treatment had the greatest increase in precentral gyrus activity (Figure 2.3).

Figure 2.3: Correlation with change in HRSD score



A significant correlation was found between the change in the severity of depression as measured by the HRSD scores and activity in the left precentral gyrus. Patients who had the greatest change in HRSD score following CBT showed the greatest increase in activity in the left precentral gyrus during processing of dysfunctional attitudes. The y-axis SSQ (sum of squares) values are a normalised statistic of the brain response.

2.3.3.2 Neural responses to regular attributions in DAS

There was no significant main effect of group or any group by time interaction effects in the neural responses to regular attributions to the DAS statements.

2.3.3.2.1 Main effect of time in MDD patients

In patients, no regions showed decreased activation from the initial to final scan, but there was main effect of time in the left cerebellum (Talairach coordinates x, y, z = -11, -74, -17; cluster size = 26 voxels, corrected p = 0.0025) which showed increased activation from weeks 0 to 16.

2.3.3.2.2 Main effect of time in healthy controls

In healthy controls, main effects of time were observed in the left lingual gyrus (BA 18), left parahippocampal gyrus, and bilateral precuneus (BA 7) (corrected $p < 0.006$) which showed reduced activation from the initial to final scans, and in the left inferior frontal gyrus (BA 10) (coordinates x, y, z = -36, 44, 3; cluster size = 36 voxels, corrected p = 0.003) which showed increased activation from the initial to final scans.

Main effects of the DAS task and group are presented in Supplementary material 1b.

2.4 Discussion

In the present study, the effects of dysfunctional thinking on regional brain activations in MDD patients as compared to healthy volunteers were examined. In addition, the neural effects of cognitive behavioural therapy on dysfunctional attitudes were also investigated.

2.4.1 Behavioural responses to DAS

The present study supports a modifying effect of CBT on dysfunctional attitudes (Haaga et al., 1991; Furlong & Oei, 2002) as patients endorsed a greater number of extreme responses to DAS statements during an acute depressive episode which normalised following CBT. Dysfunctional attitudes are

also seen to reduce following antidepressant treatment (Shankman et al., 2012), suggesting that they may be a state feature of depression. There is considerable evidence for a parallel decrease in levels of dysfunctional attitudes and depression during CBT (Persons & Burns, 1985), although dysfunctional attitudes have also been observed as a trait feature of depression (Roberts & Gamble, 2001). However, a correlation between improvements in depression severity with a reduction in extreme DAS attributions was not observed.

2.4.2 Neural responses to extreme attributions in DAS

Extreme attributions to statements showed a group by time interaction effect in the left parahippocampal gyrus. The neural correlates revealed that endorsement of dysfunctional attitudes was associated with left parahippocampal activation in both depressed patients and healthy controls, which decreased at the follow up scans in both groups but to a lesser extent in patients. The parahippocampal region along with the hippocampus and association areas of the cerebral cortex form the medial temporal lobe (MTL) system (Eichenbaum & Lipton, 2008). The flow of information from the association areas of cortex to the hippocampus is in the form of a bidirectional hierarchy of connections (Eichenbaum & Lipton, 2008). The output from the hippocampus is then returned to the parahippocampal region and to the cortical regions where the input originated (Eichenbaum & Lipton, 2008).

Depressed individuals have shown greater activation in the left parahippocampal gyrus relative to controls, during encoding of an associative learning paradigm (Werner et al., 2009) and in processing negative pictures (Sheline et al., 2009). MDD patients also show reductions in parahippocampal activation following treatment with antidepressant medication (Kennedy et al., 2001; meta-analysis: Delaveau et al., 2011). Behavioural studies of dysfunctional attitudes show higher endorsement of dysfunctional attitudes by patients relative to controls during negative mood induction (Lau et al., 2012) and significant improvement in dysfunctional thinking in patients following CBT (Warmerdam et al., 2010). To date, there has been no fMRI study that has investigated the neural correlates of dysfunctional attitudes in depression, and therefore one cannot make direct comparisons to confirm

the role of parahippocampal gyrus in dysfunctional attitudes. However, the left parahippocampal activation seems to be especially associated with negative stimuli (Iidaka et al., 2002; Surguladze et al., 2005), and activation in this region in both patients and in controls during presentation of DAS statements supports the role of the left parahippocampal gyrus in processing negative information contained in the DAS statements. The circular causality hypothesis (Burns & Spangler, 2001) proposes that dysfunctional attitudes and negative emotions have a reciprocal causal effect, which was likely induced by the DAS statements.

The parahippocampal region is also associated with contextual associations or episodic memory and shows a familiarity effect during repetition of tasks with greater activation during novel as compared to familiar tasks (O'Kane et al., 2005). The reduction in parahippocampal activation at the follow up scan for both groups is consistent with increased familiarity with repetition of the task, although patients did not demonstrate the same extent in the reduction in activation. This may perhaps reflect patients' inability to recall the task in the same manner as controls, likely due to persistent engagement and contextual associations to the DAS statements.

The main effect of group across both time points revealed greater activation in the left hippocampal gyrus, inferior parietal lobe and precuneus in patients relative to healthy controls. The inferior parietal lobe plays a prominent role in attentional processing of emotional stimuli (Pessoa et al., 2002), processing of written language (Eckert, 2004), working memory of emotional stimuli (Rämä et al., 2001), and during episodic memory retrieval (Maddock et al., 2001). The increased activation observed in MDD patients relative to controls in the inferior parietal lobe may have reflected their greater attention in the processing of DAS statements along with the retrieval of memories associated with statements presented in the DAS. The precuneus is associated with visual processing of information including the retrieval of episodic memory which is modulated by attention (Cavanna & Trimble, 2006). In depression, greater activation in left precuneus has been found in patients during presentation of sad relative to happy stimuli (Keedwell et al., 2005b), and during visual presentation of negative stimuli (Phillips et al., 2004). The increased activity in the precuneus in MDD patients likely reflects increased attention during visual processing of DAS statements.

Furthermore, improvement in the severity of depressive symptoms showed a significant positive correlation with left precentral activity. The precentral gyrus plays an important role in successful response inhibition, and patients in an acute depressive episode tend to show impaired response inhibition (Schmid et al., 2011). Increased activity in the left precentral gyrus has been reported in patients following treatment with psychotherapy (Dichter et al., 2009). Larisch et al. (1997) found significant positive correlations between dopamine (D_2) binding changes in the left precentral gyrus and an improvement in depression scores following antidepressant treatment, and the left precentral gyrus shows increased functional connectivity with the orbitofrontal cortex at baseline in subsequent responders to antidepressant treatment relative to non-responders (Lisiecka et al., 2011). The positive association between precentral activity and depression scores in the present study could reflect the improvements in inhibitory control in patients as they recovered from an acute depressive episode.

It was notable that the group differences in neural responses to extreme attributions to the DAS statements were not found with the regular attributions to DAS statements, reflecting the specificity of the neural effects to extreme attributions. However, contrary to the hypothesis, there was no evidence for increased amygdala activity in MDD patients. The probability of amygdala activation is greater during passive processing of emotional stimuli rather than tasks involving any form of attentional effort, and language is associated with a significant reduction in amygdala activity (Costafreda et al., 2008). In the present study, DAS statements were presented as sentences and participants were required to make an active judgement in response, which likely contributed to the low elicitation of amygdala responsivity with the DAS statements. Furthermore, the present study was limited by the lack of a patient group who received a placebo treatment. Therefore it is not possible to conclude with certainty that the significant difference in brain activation in patients is as a result of treatment with CBT. Future research also needs to investigate whether a reduction in dysfunctional thinking is evident with antidepressant treatment.

In summary, the present study supports findings that dysfunctional thinking is characteristic of major depression. Extreme attributions made to DAS statements are indicative of dysfunctional thinking, and depressed patients showed a significant decrease in extreme attributions, following CBT. The

main effect of group for extreme attributions showed greater activation in patients relative to controls in the left hippocampal gyrus, left inferior parietal lobule and the left precuneus. This suggests that when the DAS statements are presented, depressed patients, compared to controls, engage more in attentional processing of the statements, along with retrieval of memory associated with them. The group by time interactions for extreme attributions showed significant reductions in the parahippocampal gyrus in both groups at follow up scan, though to a lesser extent in MDD patients, perhaps reflecting improvements in dysfunctional thinking with some persistent vulnerability.

3 Neural effects of duloxetine treatment on sad and happy facial processing in major depressive disorder

The important findings from the chapter are included in the paper listed below:

Fu, C.H., Costafreda, S.G., Sankar, A., Adams, T.M., Rasenick, M.M., Liu, P., . . . Marangell, L.B. (2015). Multimodal Functional and Structural Neuroimaging Investigation of Major Depressive Disorder Following Treatment with Duloxetine. *BMC Psychiatry, 15*(1), 82-92

3.1 Introduction

Affective processing biases in depression have been extensively studied, especially in relation to emotional facial expressions (see review: Elliott et al., 2011). Acutely depressed MDD patients show impaired recognition of affective facial expressions (Surguladze et al., 2004), whereby they tend to misinterpret happy, neutral or ambiguous facial expression as being sad or less happy (Bourke et al., 2010). The affective bias is evident in several neurocognitive domains, especially in memory and attention (ex. review: Roiser et al., 2012). In particular, MDD patients show a greater recollection of negative facial expressions and decreased recall for happy facial expressions compared to neutral ones (Ridout et al., 2003). In tasks of gender recognition of negative affective stimuli, evidence suggests that MDD patients respond less accurately (Surguladze et al., 2004) and less rapidly (Fu et al., 2004, 2008a; Arnone et al., 2012) than healthy controls do. There have been few inconsistencies however, with studies showing acutely depressed MDD patients also performing as well as controls in these tasks (Sheline et al., 2001; Lawrence et al., 2004). Findings for recognition impairment for positive stimuli in depression have also been inconclusive. For instance, some behavioural studies have shown impaired performance in patients relative to healthy controls during processing of happy facial expressions (Sheline et al., 2001; Fu et al., 2007), while others have not found any group differences in either accuracy (Surguladze et al., 2005; Arnone et al., 2012) or latency (Surguladze et al., 2005). In MDD patients, impairments in processing facial expressions may be more evident when the target stimuli are presented over a long duration of time, permitting extensive processing (Mogg & Bradley, 2005).

Pharmacological treatments have been shown to improve emotional processing bias in MDD patients. A 2-week antidepressant treatment enhanced recognition of both negative as well as positive emotions in MDD patients (Tranter et al., 2009). A single dosage of reboxetine in patients also improved recognition of happy facial expressions compared to those who received placebo (Harmer et al., 2009a), while acute administration of citalopram normalised the bias towards fearful faces in recovered MDD patients (Bhagwagar et al., 2004). Even in healthy controls, a single dose of citalopram had improved their attention towards positive words though it had also increased their recognition of fearful faces (Browning et al., 2007). Furthermore, enhancement of the recognition of happy faces following

antidepressant treatment in MDD patients was linked with improvements in depressive symptoms (Tranter et al., 2009), suggesting that these emotional processing biases may be a state rather than a persistent trait-related feature of depression.

Facial processing biases in depression have been well examined with fMRI studies using standardised experimental paradigms, such as faces (Ekman & Friesen, 1976) (ex. Sheline et al., 2001; Fu et al., 2004; Keedwell et al., 2005a; Fu et al., 2007, 2008a; Suslow et al., 2010; see review: Stuhrmann et al., 2011). The affective processing tasks are typically implicit or explicit in nature. For instance, the gender decision facial task is an implicit affective processing task where the explicit instruction is to identify the gender of the face; such that the emotional expression is processed implicitly (ex. Sheline et al., 2001; Lawrence et al., 2004; Fu et al., 2004; Gotlib et al., 2005; Surguladze et al., 2005; Fu et al., 2007, 2008a; see review: Stuhrmann et al., 2011). On the other hand, in the explicit affective processing tasks, explicit instruction is to identify the emotion of the presented face which allows explicit processing of the emotion (ex. Peluso et al., 2009; Almeida et al., 2010, Scheuerecker et al., 2010; Frodl et al., 2011; see review: Stuhrmann et al., 2011). Neuroimaging studies most often use implicit affective processing tasks as they are associated with greater activations in key limbic regions within the MDD network, in particular the amygdala (Costafreda et al., 2008).

Limbic regions, especially the amygdala, are associated with emotional processing, in which the probability of amygdala activation is greater for negative rather than positive stimuli (Costafreda et al., 2008). Cross-sectional fMRI studies comparing patients and healthy control subjects have shown elevated amygdala activation in acutely depressed MDD patients, relative to healthy controls, in response to sad (Fu et al., 2004, 2007; Victor et al., 2010; Arnone et al., 2012) and fearful faces (Sheline et al., 2001), and negative pictures (Anand et al., 2007), although some studies have also found no group differences in amygdalar activity in response to negative emotional stimuli (Davidson et al., 2003; Frodl et al., 2011). Evidence suggests that emotional faces are more likely to show initial amygdala hyperactivity in patients, compared to other emotional tasks (Costafreda et al., 2008). Processing of happy facial expressions on the other hand was also associated with attenuated amygdala activation in patients compared to control subjects (Lawrence et al., 2004), providing further support for

the negative bias in depression (Surguladze et al., 2005). fMRI studies have also examined amygdala activity in at-risk individuals and in MDD patients in remission to delineate whether they are state or trait markers of depression. In response to fearful faces, high-risk individuals showed greater bilateral amygdala activation in comparison with low-risk individuals (Monk et al., 2008). Similarly, remitted MDD patients relative to controls showed elevated amygdala activity during masked sad facial processing, with a pattern of activations similar to acutely depressed patients (Victor et al., 2010). However, there is also evidence that amygdala activation in MDD patients is specific to mood state, suggesting that increased amygdala actviation may be a state marker in depression (Fu et al., 2008a; Arnone et al., 2012).

In addition to amygdala activation, the fusiform gyrus is also engaged by face processing tasks (Adolphs, 2002). A model proposed by Haxby and colleagues (2000) outlines the core face processing network that comprises of bilateral occipital regions, a face responsive region in the fusiform gyrus, and superior temporal sulcus regions. Along with this core network, facial processing is also associated with additional neural systems, such as the frontal eye regions and intraparietal sulcus for focusing attention, affective regions like the amygdala and the insula for processing emotions, and the anterior temporal lobe for retrieving semantic information associated with the face (Haxby et al., 2000). Greater fusiform activity is seen in MDD patients relative to controls during processing of negative emotional stimuli, whereas decreased fusiform gyrus activations are seen in response to positive emotional stimuli in patients (Surguladze et al., 2005; Suslow et al., 2010; meta-analysis: Groenewold et al., 2013). This supports behavioural evidence which show that patients are more likely to attend to faces of increasing sadness compared to healthy controls who in turn attend more to happy facial expressions (Joorman & Gotlib, 2007; Victor et al., 2010). In addition to amygdalar and fusiform activations, sad facial processing is also associated with activations in other limbic-subcortical structures in MDD patients, relative to controls, in particular the anterior cingulate, insula (Fu et al., 2004), hippocampus (Victor et al., 2010) and parahippocampal gyrus (Fu et al., 2004; Surguladze et al., 2005). As expected, reverse pattern of neural responses in limbic–subcortical regions is observed in response to implicit processing of happy faces, whereby MDD patients show attenuated activations in the posterior cingulate gyrus (Fu

et al., 2007), putamen (Surguladze et al., 2005), thalamus and parahippocampal region (Lawrence et al., 2004) compared to healthy control subjects.

Longitudinal fMRI studies have shown normalisation of abnormal neural responses in MDD patients in response to facial processing following treatment. Majority of these studies have focussed on the neural changes following antidepressant treatment specifically selective serotonin reuptake inhibitors (SSRI; ex. Sheline et al., 2001; Fu et al., 2004, 2007; Victor et al., 2010; Arnone et al., 2012) and relatively few studies have focussed on changes following other antidepressant classes like serotonin-norepinephrine reuptake inhibitors (ex. SNRI; Frodl et al., 2011) and psychological therapies (ex. Fu et al., 2008a). Following SSRI treatment, attenuation in activity in the amygdala (Sheline et al., 2001; Fu et al., 2004; Arnone et al., 2012), anterior cingulate (Fu et al., 2004, Victor et al., 2013), insula and putamen (Fu et al., 2004) have been observed in MDD patients. Treatment with SSRIs also seemed to improve the abnormal brain activations observed in response to positive facial stimuli in the cortico-limbic regions in MDD patients, particularly in the fusiform gyrus (Jiang et al., 2012), posterior cingulate, lingual gyrus, precuneus and the cerebellum (Fu et al., 2007).

Investigation of SNRI treatment effects on negative emotional processing in MDD have revealed similar normalization of limbic regions, particularly in the hippocampus and in other subcortical regions including the fusiform gyrus, thalamus, precuneus and the cerebellum (Frodl et al., 2011) as well as some distinct increases in the insula and anterior cingulate (Davidson et al., 2003) following venlafaxine treatment. To my knowledge, this is the first study that has examined neural responses to sad and happy facial stimuli following treatment with the SNRI, duloxetine. A study that examined duloxetine effects in MDD in response to painful stimuli observed decreases in the insula, pregenual-subgenual anterior cingulate and the dorsolateral prefrontal regions following treatment (López-Solà et al., 2010). Together, these findings suggest that SSRI and SNRI classes of antidepressants have some similar as well as distinct effects on brain activity in MDD patients.

A longitudinal fMRI study was conducted to examine the effects of duloxetine on processing sad and happy facial expressions. The main hypothesis was that treatment would be associated with

normalization of anterior cingulate cortex and amygdala activation to sad faces in patients with MDD as compared with healthy participants (Sheline et al., 2001; Fu et al., 2004; meta-analyses: Delaveau et al., 2011; Ma, 2015). It is also predicted that patients would show attenuated amygdala activity in response to happy facial expressions as compared with controls (Lawrence et al., 2004; Victor et al., 2010), which would improve with treatment (Victor et al., 2010; meta-analysis: Ma, 2015).

3.2 Methods

3.2.1 Participants

30 patients with Major Depressive Disorder and 27 healthy controls matched for age, gender and IQ were recruited through local newspaper advertisements. MDD patients were assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID; First et al., 2012), meeting criteria for single or repeated episodes of MDD without psychotic features as defined by Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). All patients had a minimum score of 18 on the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960) at the time of study entry and were free of antidepressant medication for a minimum of 4 weeks before start of the study (6 weeks for fluoxetine). Exclusion criteria were any DSM-IV-TR comorbid Axis I or II disorder including a history of substance abuse or dependence within the prior 6 months, known Alzheimer's disease or mental retardation; serious suicidal risk or risk of self-harm (Columbia-Suicide Severity Rating Scale; Posner et al., 2011); history of electroconvulsive therapy, transcranial magnetic stimulation, or vagus nerve stimulation within the past year; abnormal thyroid stimulating hormone concentration; or medical disorders known to affect central nervous system structures or function (eg. diabetes, high blood pressure, HIV and glaucoma). MDD patients were administered duloxetine 60 mg once daily for 12 weeks. At week 8, MDD patients who met criteria for remission continued on 60 mg dose, while the others could opt for an increase in dose up to 120 mg once daily.

Healthy controls with a HAMD-17 score of ≤ 7 at baseline were screened to ensure that they did not meet criteria for any psychiatric illness, neurological disorder, or heady injury resulting in a loss of consciousness. Anxiety scores of all participants were measured using the Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959). Medical reports were acquired from the General Practitioners for all participants and they were extensively examined to obtain information on antidepressant use, medication history, concomitant medications, and previous history of psychiatric illness other than major depressive disorder, previous treatment for depression or other psychiatric conditions, and any other medical or physical condition that met exclusion criteria for the study. The study was funded by Eli Lilly and company and was approved by the Cambridgeshire 4 Research Ethics Committee. The study was conducted in conformity with the Declaration of Helsinki and its amendments.

Functional MRI scans were obtained from all participants at baseline (week 0), week 1, week 8 and upon study completion (week 12). 30 MDD patients and 27 healthy volunteers (HV) were enrolled. Data from 3 healthy controls were excluded as medical reports from 2 controls revealed previous history of antidepressant use and another healthy control was diagnosed with depression one month after study completion. 23 MDD patients and 22 healthy controls completed the 12 week study. Of the 7 patients who dropped out, 4 patients discontinued as they were unable to tolerate the side effects of the drug, 1 patient suffered a serious adverse event of retinal pigment epitheliopathy which was not judged to be related to the study drug, and 2 patients did not comply with study procedures. 2 healthy volunteers dropped out of the study as they could not tolerate the scanner. Longitudinal analyses were performed with all participants who completed the study, i.e., 23 MDD patients and 22 healthy controls.

3.2.2 fMRI data acquisition

Gradient echo T2*-weighted echoplanar images were acquired depicting blood oxygenation level-dependent (BOLD) contrast. A total of 180 volumes were acquired for each for the happy and sad facial affect tasks. For each volume, 39 oblique axial slices parallel to the intercommissural plane were collected with the following parameters: slice thickness: 3 mm, slice gap: 0.3 mm, echo time

(TE): 30 milliseconds, repetition time (TR): 2000 milliseconds, flip angle: 75°, field of view: 240 mm, and matrix size: 64 x 64.

3.2.3 Experimental design

The event-related fMRI paradigm consisted of facial expressions and baseline trials presented in a pseudo-randomise order. The happy and sad faces tasks were presented as separate tasks with the sad faces following the happy faces task. Participants were shown a series of ten human faces (5 females) adapted from Ekman and Friesen's Pictures of Facial affect (Ekman & Friesen, 1976) morphed to represent faces of varying intensities: low, medium and high. The facial stimuli were presented twice at each intensity (60 faces in total), along with 12 baseline trials consisting of a crosshair visual fixation point, for a total of 72 presentations. Each stimulus was presented for duration of 3 seconds, and the interval between trials varied randomly according to a Poisson distribution, with a mean intertrial interval of 5 seconds, for a total duration of 360 seconds (6 minutes). fMRI data were acquired at weeks 0, 1, 8 and 12 (sample response file is available in Supplementary material 2).

During each trial, subjects were instructed to specify the gender of the face. Responses were made by pressing a button in the scanner (right button to indicate a male face and left to indicate a female face) with their forefinger and third finger. Latency (response time) and accuracy of gender decision were recorded for each trial.

3.2.4 fMRI data analysis

Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK; Ashburner et al., 2012) was used to pre-process and analyse the task-related fMRI data using default settings. The images were realigned to correct for motion artefacts, spatially normalized to the Montreal Neurological Institute (MNI) template, and smoothed using an 8mm full-width at half maximum (FWHM) Gaussian kernel filter. First-level analysis was performed using the general linear model, accounting for serial autocorrelations by applying an autoregressive model. Stimuli presentation was modelled as individual events and the first level analysis produced contrast images

relevant to the main contrast of interest (sad faces or happy faces *vs* crosshair baseline). Second-level analysis employed a random-effects model to examine the main effect of group (MDD *vs* HV across all time points), main effect of time (linear changes over weeks 0, 1, 8, 12) and the group x time interaction. Independent samples t-tests were also used to compare scanning data at a particular time point between groups. Paired t-tests was also performed in patients and controls separately to compare changes between two specified time points. To identify brain regions associated with clinical improvement, percentage change in HAMD-17 scores after 12 weeks of treatment was regressed on change in BOLD response, estimated by subtracting the t map for bold response at week 0 from the corresponding map at week 12. Inference on whole-brain statistical images was conducted using the general linear model (GLM) and cluster-wise family-wise error rate (FWER) with $p < 0.05$ corrected for multiple comparisons. In addition to the whole brain approach, a region-of-interest analysis was also performed by other investigators of this study to examine mean percentage signal change in BOLD response, by comparing patients and controls, from baseline to week 12 in bilateral amygdala in response to sad facial expressions (Fu et al., 2015).

3.3 Results

3.3.1 Demographic results

Age, gender and IQ were not significantly different between patients and controls (all $p > 0.4$) (Table 3.1). Patients had significantly higher HAMD scores compared to controls ($p < 0.001$) which decreased following treatment ($p < 0.05$). Upon study completion, 18 patients met criteria for a clinical response to treatment defined by a minimum of 50% reduction in HAMD-17 score and 16 patients met criteria for clinical remission defined as a HAMD-17 score of 7 or less at the end of treatment. Information on other clinical characteristics of patients such as illness onset, course, and duration, and treatment history were unavailable.

Table 3.1: Demographic and clinical characteristics

Characteristic	Patients with Depression (N=23)		Healthy Volunteers (N=22)	
	Mean	SD	Mean	SD
Age (years)	39.83	11.21	39.09	10.29
Full IQ	107.83	10.71	108.18	13.75
Verbal IQ	110.00	9.86	108.45	12.56
Performance IQ	103.17	14.43	106.36	15.31
HAMD (baseline)	21.96	2.85	0.32	1.09
HAMD (week 12)	6.87	4.62	0.59	1.22
HAMA (baseline)	20.74	5.39	*	*
HAMA (week 12)	7.52	4.41	0.50	1.01

* HAMA not done for healthy volunteers at baseline

3.3.2 Behavioural results

3.3.2.1 Behavioural results for sad facial affect processing

ANOVA showed a main effect of intensity on latency ($F_{2, 86} = 14.96$, $p < 0.001$): all participants were slower at the high intensity of sad facial expressions. There were no other main effects of group, time or any significant second or third order interaction effects on latency (Table 3.2).

For accuracy of explicit gender recognition, there was a significant main effect of time on accuracy ($F_{3, 129} = 3.54$, $p = 0.017$) in which all subjects made more errors with the successive scans over time. There was also a main effect of intensity on accuracy ($F_{2, 86} = 3.74$, $p = 0.028$) in which participants made most incorrect responses while responding to facial stimuli portraying intense degrees of sadness compared to neutral ones. There were no main effects of group, nor any significant second or third order effects (Table 3.2).

Table 3.2: Behavioural performance on sad facial expression task

Intensity of sad expressions	MDD Patients N=23	Healthy Controls N=22
Baseline		
Reaction time		
Low intensity	958.02 (221.77)	958.44 (299.48)
Medium intensity	986.25 (211.70)	955.54 (250.73)
High intensity	1041.08 (269.87)	984.27 (280.97)
Accuracy		
Low intensity	17.30 (1.10)	17.77 (0.86)
Medium intensity	17.65 (1.02)	17.81 (0.39)
High intensity	17.30 (1.02)	17.59 (1.22)
Week 12		
Reaction Time		
Low intensity	970.39 (283.65)	934.20 (277.43)
Medium intensity	958.98 (260.96)	935.67 (267.81)
High intensity	1015.36 (290.47)	959.64 (272.21)
Accuracy		
Low intensity	15.91 (3.32)	17.36 (1.76)
Medium intensity	16.26 (3.00)	17.40 (1.76)
High intensity	16.04 (3.57)	17.04 (1.78)

Mean values are presented with standard deviation in parenthesis

3.3.2.2 Behavioural results for happy facial affect processing

ANOVA showed a main effect of time on latency ($F_{3, 123} = 3.3$, $p = 0.023$), with all participants responding at a faster rate over time (Table 3.3). There were no other significant main effects of group, intensity, or group by time interactions on latency.

Accuracy of gender recognition showed significant intensity by group interaction ($F_{2, 82} = 3.85$, $p = 0.025$), as MDD participants showed the greatest errors for the medium intensity of expression while healthy participants had greater errors for the lowest intensity. There was also a significant interaction effect of intensity by time ($F_{6, 246} = 2.86$, $p = 0.01$) in which all participants made the most errors for the medium and highest intensities at the final (week 12) scan while there were few changes in accuracy for the lowest intensity with successive scans over time. There were no other significant main effects of group, time, or any other second or third order effects on accuracy (Table 3.3).

Table 3.3: Behavioural performance on happy facial expression task

Intensity of happy expressions	MDD Patients N=23	Healthy Controls N=21*
Baseline		
Reaction Time		
Low intensity	1086.76 (381.10)	975.88 (192.34)
Medium intensity	1122.31 (413.32)	1006.35 (189.69)
High intensity	1117.18 (420.35)	981.45 (171.85)
Accuracy		
Low intensity	17.52 (1.16)	17.29 (1.27)
Medium intensity	17.17 (0.83)	17.62 (0.92)
High intensity	17.65 (0.77)	17.71 (1.05)
Week 12		
Reaction Time		
Low intensity	1000.69 (291.11)	893.88 (155.87)
Medium intensity	953.73 (212.64)	884.76 (142.69)
High intensity	974.08 (244.75)	935.35 (140.24)
Accuracy		
Low intensity	17.35 (1.02)	17.33 (1.90)
Medium intensity	16.57 (1.92)	17.19 (1.77)
High intensity	16.87 (2.18)	17.33 (1.79)

Mean values are presented with standard deviation in parenthesis. * Behavioural response only available for 21 healthy controls.

3.3.3 Functional MRI results

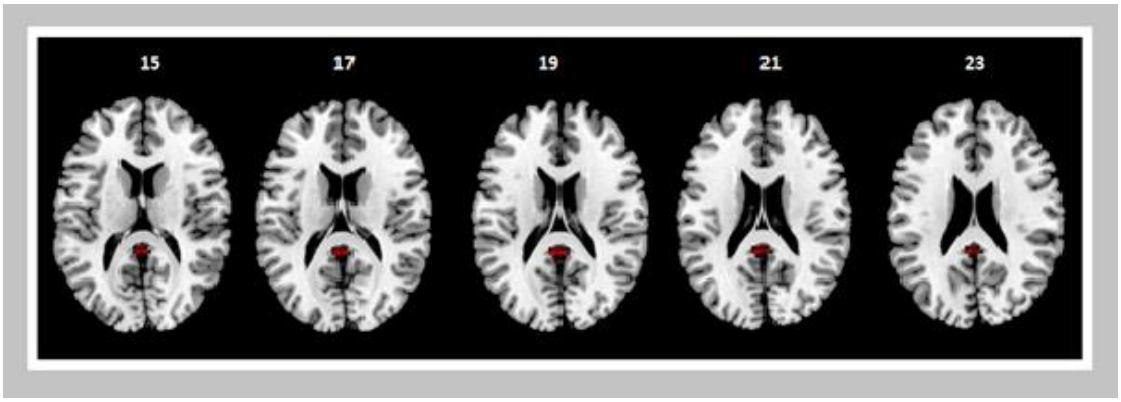
3.3.3.1 Functional MRI results for sad facial affect processing

Contrary to the hypothesis, the whole brain results did not reveal any significant group by time interaction effects nor any main effect of group. In MDD patients, there was a main effect of time with a significant increase in the BOLD contrast response to the mean of the medium and high intensity of expressions in the posterior cingulate (x = -3, y = -43, z = 19; 221 voxels; peak T = 4.50; $p_{(FWE\ corrected)} = 0.010$) (Figure 3.1), while healthy participants showed a trend towards a decrease in the orbitofrontal region (x = 45, y = 29, z = -11; 118 voxels, T = 4.61, $p_{(FWE\ corrected)} = 0.068$). When medium and high intensity faces were considered separately, there was a main effect of time in MDD patients with a significant increase in the BOLD response to the medium intensity facial expression in

the posterior cingulate (x= -3, y = -43, z = 22; 298 voxels; peak T = 4.77; $p_{(FWE\ corrected)} = 0.002$), while healthy volunteers showed a decrease in the fusiform gyrus in response to high intensity of expressions (x = -36, y = -82, z = -17; 138 voxels; peak T = 4.39; $p_{(FWE\ corrected)} = 0.050$).

The region-of-interest analysis did not reveal any significant difference between groups in the change in BOLD response from baseline to week 12 in the bilateral amygdala in response to sad facial expressions (Fu et al., 2015).

Figure 3.1: Main effect of time in MDD patients in the posterior cingulate gyrus

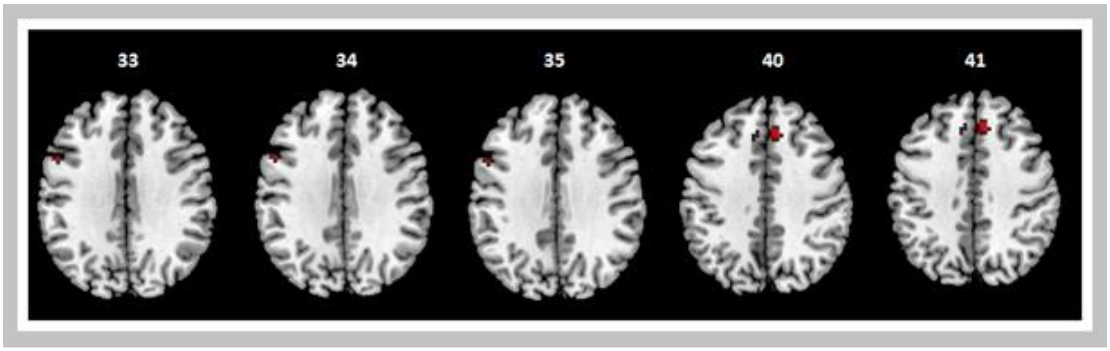


MDD patients showed a significant increase with time in the BOLD contrast response to the mean of the medium and high intensity of expressions in the posterior cingulate (x = -3, y = -43, z = 19; 221 voxels; peak T = 4.50; $p_{(FWE\ corrected)} = 0.010$). Transverse sections are depicted from z co-ordinates 15 to 23.

3.3.3.2 Functional MRI results for happy facial affect processing

There were neither group by time interaction effects nor main effects of group. There were no main effects of time among patients with MDD, but healthy participants showed a significant decrease with time in response to the mean of medium and high intensity expressions in the mid cingulate gyrus (x = 9, y = 29, z = 40; 315 voxels, peak T = 4.27; $p_{(FWE\ corrected)} = 0.002$) and precentral region (x = -51, y = 11, z = 34; 190 voxels; peak T = 4.08; $p_{(FWE\ corrected)} = 0.018$) (Figure 3.2), as well as approaching significance in the thalamus (x = 3, y = -13, z = 10; 118 voxels; T = 4.12; $p_{(FWE\ corrected)} = 0.070$).

Figure 3.2: Main effect of time in controls in the mid cingulate and precentral regions



Healthy participants showed a significant decrease with time in the BOLD contrast response to the mean of the medium and high intensity of expressions in the mid cingulate gyrus gyrus (x = 9, y = 29, z = 40; 315 voxels, peak T = 4.27; $p_{(FWE\ corrected)} = 0.002$) and precentral region (x = -51, y = 11, z = 34; 190 voxels; peak T = 4.08; $p_{(FWE\ corrected)} = 0.018$). Transverse sections are depicted from z co-ordinates 33 to 41.

3.3.3.3 Functional MRI results for exploratory analysis on happy facial affect processing

Exploratory analyses (paired t-tests) were also performed in MDD patients to examine changes in brain activity at different time points (week 1, week 8 and week 12) from baseline. Findings showed decreases in BOLD responses in the inferior frontal gyrus after both 1 and 8 weeks of treatment. Additional changes were observed in the insula and the angular gyrus after 1 week of treatment. However, compared with baseline, no regions showed significant changes in activity following 12 weeks of treatment (Table 3.4).

Table 3.4: Longitudinal analysis in MDD patients following 1 and 8 weeks of treatment

Brain Region	MNI coordinates			Voxels	*Z* value	*P* value
	x	y	z			
Week1 < Baseline						
Neutral vs cross						
L Angular Gyrus	-48	-52	34	140	6.60	0.028
R Insula	39	26	-2	263	6.37	0.002
L Inferior Frontal Gyrus (Orbital Part)	-39	41	-11	118	6.33	0.047
Week 8 < Baseline						
Neutral vs cross						
L Inferior Frontal Gyrus (Orbital Part)	33	20	-20	261	6.78	0.003
R Inferior Frontal Gyrus (Orbital Part)	-33	20	-23	192	6.28	0.010

3.4 Discussion

The present study investigated the behavioural and neural correlates of facial processing bias in medication-free depressed patients and following treatment with the SNRI duloxetine. Behavioural responses showed limited differences between the groups, especially for sad facial processing.

3.4.1 Neural correlates of treatment during processing of sad facial expressions

Contrary to the hypothesis, the neural correlates did not reveal a significant group by time interaction in response to sad facial expressions. A meta-analysis of the neural effects of antidepressant treatment revealed a consistent normalisation of limbic activity particularly in the amygdala, hippocampus, parahippocampal region and the anterior cingulate gyrus in MDD patients during negative emotional processing (Delaveau et al., 2011), however these responses were typically observed following treatment with selective serotonin reuptake inhibitors (Sankar & Fu, in press). In MDD patients, attenuation of amygdala activity following SSRI treatment is consistent with the density of serotonin receptors within the amygdala (Xu and Pandey, 2000) which are a target of action for SSRIs (Jiang et al., 2011). Moreover, in MDD patients, normalization of amygdala activity has been reported even before clinical improvements (Godlewska et al., 2012), reflecting a therapeutic mechanism of action of SSRIs. On the other hand, very few functional imaging studies have investigated the effects of SNRI on emotional processing; therefore our understanding of whether the neural correlates of different antidepressant classes is comparable remains unclear. Preliminary investigations on healthy controls revealed that a single dose of SSRI led to decreased amygdala responses to emotional faces, while acute administration of the Norepinephrine Reuptake Inhibitor (NRI) medication increased activation in medial and frontal areas (Outhred et al., 2013). In patients, treatment with the SNRI venlafaxine was associated with increases in the limbic regions, particularly the insular and anterior cingulate regions (Davidson et al., 2003), as well as decreases in the subcortical and cortical regions (Frodl et al., 2011) in response to negative affective paradigms. It is postulated that SSRI may have early attenuating effects on emotional reactivity, while NRI is associated more with emotional regulation (Outhred et al., 2013).

The present study showed significant increases in the posterior cingulate in MDD patients with time during sad facial processing. The posterior cingulate is an important part of the default mode network (Fransson & Marrelec, 2008; Leech et al., 2011) and has functional connections with the limbic system (review Leech & Sharp, 2014). It is also associated with episodic memory (Wagner et al., 2005), shows activation in response to affective stimuli, both negative and positive, (Maddock et al., 2003) and plays a key role in regulating attention (Hahn et al., 2007; review: Leech & Sharp, 2014). Resting state studies using PET have revealed increases in the posterior cingulate with venlafaxine (Kennedy et al., 2007). Moreover, in MDD patients who received either mirtazapine or venlafaxine, increased pre-treatment activity in the posterior cingulate during sad facial processing was associated with better response to treatment (Samson et al., 2011). Even in healthy controls, acute administration of NRI was associated with increased posterior cingulate activity during processing of emotional pictures (Outhred et al., 2013). A comparison of SSRI and NRI classes of antidepressants in healthy controls showed that acute administration of reboxetine (NRI) led to increases in the posterior cingulate, a finding not seen with citalopram (SSRI) which was more associated with prefrontal modulations (Brühl et al., 2010). However, there have been concerns over the clinical efficacy of reboxetine in alleviating depressive symptoms. A study that analysed 13 published and unpublished acute placebo controlled and/or SSRI controlled treatment trials concluded that reboxetine was ineffective as an antidepressant (Eyding et al., 2010). This was contrary to findings from two earlier analyses of merely placebo-controlled studies that found greater efficacy of the drug compared with placebo (Ferguson et al., 2002; Montogomery et al., 2003). In MDD patients, SSRI treatment was specifically associated with decreases in the posterior cingulate region (meta-analysis: Delaveau et al., 2011). Thus, dual acting antidepressants that modulate noradrenergic and serotonergic systems have differential neural effects to SSRI that modulate specifically the serotonergic system. Increase in posterior cingulate activity following treatment with duloxetine in the present study may reflect a specific treatment effect of antidepressants that modulate noradrenergic systems.

3.4.2 Neural correlates of treatment during processing of happy facial expressions

The present study did not reveal a significant group by time interaction effect in the amygdala for happy facial expressions, contrary to the hypothesis. A meta-analysis of functional neuroimaging studies in healthy controls found greater probability of amygdala activation for negative stimuli, such as those that evoke fear and disgust relative to happiness (Costafreda et al., 2008). Even in MDD patients, abnormal amygdala activity in response to sad stimuli has been widely reported, while for happy faces, differences in amygdalar activity have been less replicated (review: Stuhrmann et al., 2011). In particular, previous neuroimaging studies that examined neural correlates of positive emotional stimuli have failed to observe significant group differences (Fu et al., 2007; Arnone et al., 2012; Rosenblau et al., 2012) or any group by time interaction effects (Davidson et al., 2003; Fu et al., 2007) in the amygdala.

Additional exploratory analysis in MDD patients examining changes in brain activity following 1, 8 and 12 weeks of duloxetine treatment showed that compared with baseline scans, inferior frontal gyrus activity reduced after both 1 and 8 weeks of treatment in response to neutral faces (Table 3.4). The right inferior frontal gyrus is especially activated during assessment of facial expressions (Nakamura et al., 1999) and in healthy controls, activation of inferior frontal gyrus is seen in response to neutral faces in comparison with non-facial stimuli (ex. scrambled images) (Kesler et al., 2001). In MDD patients, a meta-analysis of emotional processing studies found significant decreases in the right inferior frontal gyrus with antidepressant treatment (Delaveau et al., 2011). This is consistent with findings from the present study, although potential confounding effects of time and repeated neuroimaging scans must be considered. I expected to find greater change in regional brain activity in MDD patients following study completion (week 12), however paired-t-test did not reveal any significant difference in brain activity in patients between week 12 and baseline scans. It is proposed that antidepressants that potentiate the noradrenergic systems seem to have earlier effects on emotional processing and less consistent long term effects on negative emotional processing which is usually seen with SSRI treatment (Pringle et al., 2013).

Limitations of the present study include the small sample size, which may have led to insufficient power to detect all group differences at the neural level. Also, the high response rate in this study limited the power to detect differences between treatment responders and patients with a more treatment resistant form of depression, which may be associated with distinct neural correlates (Anand et al., 2005; Fu et al., 2015). Finally, the absence of a treatment group receiving placebo limits our attribution of effects to the antidepressant medication as opposed to changes associated with clinical improvement, although the potential effects of time were accounted for by having HV participants undergo scans at the same time points as MDD patients.

In summary, the functional neuroimaging correlates showed increases in the posterior cingulate gyrus in MDD patients with treatment. This is consistent with findings that show increases in this region with antidepressants that potentiate the noradrenergic systems (Kennedy et al., 2007; Brühl et al., 2010; Outhred et al., 2013). Results from this study reflect some distinct effects of the SNRI class of antidepressants, however, further investigation with a larger sample is required to confirm obtained findings.

4 Neural effects of duloxetine treatment on working memory in major depressive disorder

4.1 Introduction

Major depression is often associated with cognitive deficits which are evident across numerous neuropsychological domains. Patients with MDD show impairments in attention (Trichard et al., 1995; Austin et al., 1999; Ravnkilde et al., 2002; Porter et al., 2003; Donaldson et al., 2007; Iverson et al., 2009), memory, both immediate (Brand et al., 1992; Ravnkilde et al., 2002; Porter et al., 2003; Walter et al., 2007; Iverson et al., 2009) as well as delayed (autobiographical memory: Young et al., 2012), and other executive functions such as decision making (Murphy et al., 2001). Cognitive impairments are seen in MDD patients, very early in the course of the disorder, even in their first episode (meta-analysis: Lee et al., 2012). Furthermore, these may be present in individuals at familial risk (Christensen et al., 2006), and have enduring effects in recovered patients (Weiland-Fiedler et al., 2004; Paelecke-Habermann et al., 2005; Smith et al., 2006; Reppermund et al., 2009). A recent meta-analysis, investigating a single neuropsychological test battery, the Cambridge Neuropsychological Test Automated Battery, (CANTAB), found impairments in memory and attention in acutely depressed as well as remitted MDD patients (Rock et al., 2014), suggesting that cognitive deficits may be present in patients independent of their mood state. Impairments were also evident in euthymic MDD patients in a range of cognitive domains that included inhibitory control, executive functions, memory and processing speed (Bora et al., 2013). However, both studies included elderly populations with MDD and age is likely to have a significant effect on cognitive functioning in MDD patients (Porter et al., 2007). Moreover, both Rock et al. (2014) and Bora et al. (2013) included patients with late-onset depression in their analyses and the magnitude of deficits in attention and memory in euthymic patents were generally modest when late onset depression was excluded (Bora et al., 2013).

Presence of comorbid disorders may also influence the extent of cognitive impairments in major depression. For instance, psychiatric comorbidity was found to be a strong predictor of impaired cognitive function (Baune et al., 2009), and the presence of psychotic symptoms was associated with poorer attentional performance in MDD patients (Nelson et al., 1998; Schatzberg et al., 2000). Other clinical factors that may be linked to the magnitude of cognitive impairments in MDD patients include illness severity and number of depressive episodes, although they require further investigation. For

example, while some studies have found negative associations between illness severity and cognitive functioning, such as with executive functions (Paelecke-Habermann et al., 2005; Sheline et al., 2006; McDermott & Ebmeier, 2009), language processing (Sheline et al., 2006; McDermott & Ebmeier, 2009), working and episodic memory (Sheline et al., 2006; McDermott & Ebmeier, 2009), others have found no significant associations between working memory performance (Gruber et al., 2011), or executive functions (Porter et al., 2003; Schmid & Hammar et al., 2013) and severity of depression. It has also been suggested that increase in number of episodes may be associated with further decline in cognitive control (Vanderhasselt & De Raedt, 2009), however findings have been inconsistent with results showing no such relationship with working memory (Lyche et al., 2010; Schmid & Hammar et al., 2013).

Apart from patient characteristics, pharmacological effects on cognitive functions needs to be considered when examining MDD patients (ex. Kyte et al., 2005; Boeker et al., 2012). In general, cognitive impairments are seen to improve following successful treatment with SSRIs (Koetsier et al., 2002; Herrera-Guzman et al., 2009), SNRIs (Herrera-Guzman et al., 2009) or tricyclic antidepressants (Koetsier et al., 2002), although some persistent residual impairments are also found in recovered individuals (Paelecke-Habermann et al., 2005; Reppermund et al., 2009).

It has been postulated that some of the cognitive deficits seen in MDD patients are due to dysfunctions in the central executive component of working memory (Channon et al., 1996). Working memory is a brain system which permits transient holding and manipulation of information, important for higher level processing such as comprehension, learning and memory (Baddeley, 1992). Functional magnetic resonance imaging (fMRI) studies of working memory in healthy controls have shown involvement of the lateral prefrontal cortex (PFC), especially the ventrolateral prefrontal cortex (VLPFC)/inferior frontal gyrus (IFG) and the dorsolateral prefrontal cortex (DLPFC), and also the posterior parietal cortex (Owen et al., 2005). The subregions of the PFC are involved in specific working memory related functions, for instance, the VLPFC is thought to be involved in the simpler processes, such as encoding and retrieval of information (Petrides, 2000) whereas active monitoring and manipulation of information recruits the DLPFC (D'Esposito et al., 1998; Petrides 2000).

Moreover, the prefrontal regions show load dependent activations, with greater engagement of these regions with increasing task difficulty (IFG: Braver et al., 1997; DL PFC: Braver et al., 1997; Manoach et al., 1997).

Typically neuroimaging studies have used the n-back task to investigate working memory processes in healthy subjects (Nystrom et al., 2000; Rämä et al., 2001; Hautzel et al., 2002; Ragland et al., 2002; Zurowski et al., 2002). In the n-back task, subjects indicate whether a given verbal or nonverbal stimulus in a sequence matches the one presented n trials previously. The n-back tasks require 'on-line' monitoring and manipulation of information held in working memory (Owen et al., 2005), however such designs do not differentiate maintenance dependent load activation from other working memory processes such as encoding and probe related effects (Narayanan et al., 2005). In the present study, a modified version of the Sternberg Item Recognition Task (Sternberg, 1966) was used in which subjects, after maintaining a sequence of letters across a delay period are asked to judge whether the probe letter belonged to the original sequence of letters.

It is argued that the Sternberg task may be more similar to a visuospatial recognition memory task rather than a working memory task especially when the task does not require participants to recall the sequence of digits in the order of their presentation (Corbin & Marquer, 2013). Unlike the classic Sternberg paradigm used in the Corbin & Marquer (2013) study, in which subjects are shown the probe digit shortly after a brief delay (typically 1-2 seconds), the present study used a modified version of the task that incorporated a variable maintenance period lasting between 5 and 15 seconds. Thus, in this study, the stimuli needed to be actively maintained over a minimum duration of 5 seconds, not merely recognised, and working memory load was manipulated as a function of the duration of the delay phase (5 seconds *vs* 15 seconds). Moreover, to prevent direct visual match or recognition with the encoded stimuli, items were presented as uppercase letters (eg: A Q B J H E) while the probe stimuli were in lower case, a method also employed in other Sternberg-type working memory studies (ex. Bunge et al., 2001; Schneider-Garces et al., 2010). The Sternberg task is seen as a good measure of the ability to search and maintain information in the working memory (Barch et al., 2011) and engages more in stimulus maintenance, compared to the n-back which emphasizes

manipulation of information. Modifications to the Sternberg task for fMRI compatibility have consistently activated regions associated with working memory maintenance such as the ventrolateral prefrontal and posterior parietal regions (Veltman et al., 2003; Narayanan et al., 2005), and also activates the DLPFC, which is thought to be involved in manipulations of information, at higher loads (Manoach et al., 1997). Preliminary findings from neuroimaging studies (ex Veltman et al., 2003 and Narayanan et al., 2005) have also revealed that maintenance and manipulation tasks activate very similar distributed area of the working memory network. In the present study, the modified Sternberg paradigm was used to measure working memory, as opposed to the n-back task, as it permitted the delineation of neural responses during encoding, maintenance and retrieval of information (see Narayanan et al., 2005). In line with previous findings, it is expected that the Sternberg task used here would engage a network of working memory regions, such the inferior frontal and DLPFC, similar to what is seen with the n-back tasks. However, large scale neuroimaging studies that compare the n-back with the modified Sternberg task, such as the one used here, are required to examine whether maintenance and manipulation working memory tasks reliably engage the same network of regions. Novel paradigms of working memory that allow investigation of both maintenance and manipulation related brain activations, yet permit dissociation from other working memory processes such as encoding and retrieval would help understand the neuropsychological underpinnings of working memory impairments in depression more accurately. Moreover, the neural correlates of another feature of depression, i.e. autobiographical memory impairments, whereby MDD patients show deficits in recalling specific personal memories, have biased recollection of negative memories, or tend to avoid or supress painful personal memories (review: Dalgleish & Werner-Seidler, 2014), have been hardly explored (Young et al., 2012) and calls for further investigation.

Few cross-sectional neuroimaging studies have examined the neural correlates of working memory in MDD patients, including patients taking medication (ex. Harvey et al., 2005; Rose et al., 2006; Walter et al., 2007; Fitzgerald et al., 2008), and patients with comorbid illnesses (ex. Matsuo et al., 2007). fMRI investigations of group differences in neural activity revealed greater recruitment of regions associated with working memory in acutely depressed MDD patients relative to healthy controls. For

instance, processing of working memory using n-back tasks was associated with increased activity in patients relative to healthy controls in the DLPFC/middle frontal gyrus (Harvey et al., 2005; Matsuo et al., 2007; Walter et al., 2007; Fitzgerald et al., 2008), inferior frontal gyrus (Harvey et al., 2005; Walsh et al., 2007; Fitzgerald et al., 2008) and temporo-parietal regions (Walsh et al., 2007; Fitzgerald et al., 2008). In the anterior cingulate, however, there has been evidence of increased activity bilaterally in MDD patients (Fitzgerald et al., 2008), no significant mean group differences (Matsuo et al., 2007), as well as decreases in both groups, but with significantly greater deactivation in controls compared to patients in the rostral part (Rose et al., 2006). The neurobiological differences between patients and controls during working memory were evident in the absence of behavioural differences (Harvey et al., 2005; Rose et al., 2006; Matsuo et al., 2007; Fitzgerald et al., 2008). These findings suggest that MDD patients show greater prefrontal engagement compared with healthy controls, to maintain performance on working memory tasks.

Majority of the studies on working memory in MDD have used the n-back task (ex. Harvey et al., 2005; Rose et al., 2006; Matsuo et al., 2007; Walsh et al., 2007; Fitzgerald et al., 2008), and relatively few studies have used paradigms that allow dissociation of encoding and probe related effects. Preliminary investigations of PET and fMRI studies have revealed encoding and retrieval related increases in the inferior frontal gyrus (encoding: Bremner et al., 2004; recognition: Dietsche et al., 2014), as well as decreases in the anterior cingulate regions (encoding: Bremner et al., 2004; Kelley et al., 2013; retrieval: Kelley et al., 2013) in MDD patients relative to healthy controls. There have also been some inconsistencies, for instance, the middle frontal gyrus has shown increases (Bremner et al., 2004; Dietsche et al., 2014), as well as decreases (Kelley et al., 2013), while the parietal regions have shown both increases (Bremner et al., 2004), decreases (Werner et al., 2009) or no regional differences (Kelley et al., 2013) in MDD patients compared with controls during encoding. The hippocampus is usually associated with memory retrieval, and studies have shown dysfunctional activations (Fairhall et al., 2010) in MDD patients as well as no significant group differences (Kelley et al., 2013; Werner et al., 2009). The differences in the neural responses in these studies may be in part due to the variations in sample characteristics, neuroimaging paradigm as well as the analysis

methods. For instance, Bremner et al. (2004) used PET imaging to examine functional correlates of working memory impairments in depression, while all other studies (ex. Werner et al., 2009; Fairhall et al., 2010; Kelley et al., 2013; Dietsche et al., 2014) employed fMRI methods. Moreover, except for Bremner et al. (2004), all other studies included patients already on antidepressant medication (Werner et al., 2009; Fairhall et al., 2010; Kelley et al., 2013; Dietsche et al., 2014). Additionally, Dietsche et al. (2014) and Kelley et al. (2013) also included patients with comorbid disorders. With respect to paradigms, both Kelley et al. (2013) and Bremner et al. (2004) used verbal tasks, while Dietsche et al. (2014), Werner et al. (2009) and Fairhall et al. (2010) presented the items as faces. Furthermore, Kelley et al. (2013) and Fairhall et al. (2010) used a region-of-interest approach, which provides greater power to detect a difference compared to whole brain approaches (Costafreda et al., 2008), but may not detect all possible neural effects.

In order to study neural responses that are state specific from trait related features, fMRI studies have also investigated working memory impairments in remitted patients (Schoening et al., 2009; Kerestes et al., 2012; Norbury et al., 2014) and in people at familial risk for developing depression (Mannie et al., 2010). Although, at-risk individuals (Mannie et al., 2010) and remitted patients (Schoening et al., 2009; Kerestes et al., 2012; Norbury et al., 2014) did not differ from healthy controls in their behavioural responses on a verbal (Schoening et al., 2009; Mannie et al., 2010; Norbury et al., 2014) or an affective (Kerestes et al., 2012) memory task, changes in neural responses were observed. For example, in response to verbal working memory, at risk individuals showed increased load-response activity in the lateral occipital, superior temporo-parietal regions (Mannie et al., 2010), while remitted patients showed increased activity in the hippocampal region (Norbury et al., 2014) and in anterior and posterior cingulate cortex (Schoening et al., 2009) in comparison with control subjects. Incorporation of an emotional distractor in a working memory task was associated with increased DLPFC activity in remitted patients compared to controls in response to negative stimuli, while the opposite effect was observed in response to positive ones (Kerestes et al., 2012). Together, these findings suggest that the neural responses to working memory may be trait markers for depression that are present independent of task performance.

Treatment related changes on the neural correlates of working memory have not been widely examined. Much of the research performed to date is focussed on the effects of antidepressant medication on affective stimuli (see meta-analysis: Delaveau et al., 2011), and the neural correlates of treatment on cognitive processes in MDD patients remains unclear. In MDD patients, examination with PET imaging showed that antidepressant treatment was associated with increased ACC activity for both neutral and emotional declarative memory (Bremner et al., 2007). Moreover, investigations using functional MRI revealed that lower load response activity in the ACC at baseline on a verbal working memory task was associated with better response to fluoxetine (Walsh et al., 2007). The anterior cingulate is an important part of the limbic system, but specific subdivisions of the ACC, specifically the dorsal division is activated by cognitively challenging tasks such as the Stroop, divided-attention and many working memory tasks (Bush et al., 2000). Increase in anterior cingulate activity following antidepressant treatment is perhaps indicative of improvement in cognition in MDD patients. In addition to modulation in the anterior cingulate, antidepressant treatment is also associated with increased load response activity in the caudate and thalamus in response to verbal working memory (Walsh et al., 2007). Even in healthy individuals who underwent a sad mood induction, immediate administration of duloxetine led to increased activity in the amygdala during mood incongruent memory retrieval, as well as decreased activity in the putamen, middle frontal and cingulate gyri during formation of congruent and incongruent memory (Tendolkar et al., 2011), suggesting improvement in mood congruent biases with antidepressant treatment. Changes in neural activation with treatment were evident even in the absence of improvement in behavioural performance (Walsh et al., 2007; Tendolkar et al., 2011).

Although evidence from cross-sectional studies show modulations in the prefrontal and anterior cingulate regions in MDD patients relative to controls during working memory, it is unclear whether such changes are evident across the different working memory processes (i.e. encoding, rehearsal and retrieval stages). Moreover, the effects of antidepressants on the neural correlates of working memory have not been extensively studied. Thus, based on the limited findings, it is hypothesised that patients would show increased activity in the prefrontal regions, primarily the inferior frontal gyrus

and the middle frontal gyrus/dorsolateral prefrontal cortex in comparison to controls during encoding, maintenance and retrieval that normalised following antidepressant treatment. In addition, patients were also expected to show improved ACC activity with treatment.

4.2 Method

4.2.1 Participants

Participants who took part in the happy and sad facial expression tasks (Chapter 3) also responded to the working memory paradigm, the neural correlates of which is examined in this chapter. As described in Chapter 3, 30 patients with MDD and 27 healthy controls matched for age, gender and IQ were recruited through local newspaper advertisements. Patients with MDD assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV; First et al., 2012) met criteria for single or repeated episode MDD without psychotic features as defined by Diagnostic Statistical Manual of Mental Disorders, Fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000). All patients had a minimum score of 18 on the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960) at the time of study entry and were free of antidepressant medication for a minimum of 4 weeks before start of the study (6 weeks for fluoxetine). Exclusion criteria were any DSM-IV-TR comorbid Axis I or II disorder including a history of substance abuse or dependence within the prior 6 months, excluding nicotine and caffeine; known Alzheimer's disease or mental retardation; serious suicidal risk or risk of self-harm (Columbia-Suicide Severity Rating Scale; Posner et al., 2011); history of electroconvulsive therapy, transcranial magnetic stimulation, or vagus nerve stimulation within the past year; abnormal thyroid stimulating hormone concentration; or medical disorders known to affect central nervous system structures or function. MDD patients were administered duloxetine, a serotonin norepinephrine reuptake inhibitor (60 mg once daily) for 12 weeks. At week 8, patients with MDD who met criteria for remission continued on 60 mg dose, while the others could opt for an increase in dose (up to 120 mg, once daily) (Fu et al., 2015).

Healthy controls with a HAMD-17 score of ≤7 at baseline were screened to ensure that they did not meet criteria for any psychiatric illness, neurological disorder, or heady injury resulting in a loss of consciousness (Fu et al., 2015). Medical reports were acquired from the General Practitioners for all participants and they were extensively examined to obtain information on antidepressant use, medication history, concomitant medications, previous history of psychiatric illness other than major depressive disorder, previous treatment for depression or other psychiatric conditions, and any other medical or physical condition that met exclusion criteria for the study. The study was funded by Eli Lilly and company and was approved by the Cambridgeshire 4 Research Ethics Committee. The study was conducted in conformity with the Declaration of Helsinki and its amendments. Functional MRI scans were obtained from participants at baseline (week 0), week 1, week 8 and upon study completion (week 12). 23 patients with MDD (13 Males, 10 Females) and 22 healthy volunteers (12 Males, 10 Females) completed the study (Fu et al., 2015).

4.2.2 Experimental design

The Sternberg item recognition task was used to assess working memory in participants. During the encoding phase, subjects viewed a set of six letters that was presented for duration of 3 seconds. Following this, a blank screen appeared (rehearsal phase) that lasted either 5 seconds (short maintenance) or 15 seconds (long maintenance). The participants were then presented with a single letter for 2 seconds and they were required to indicate with a button press whether the target letter was part of the initial set of letters. The target letter was contained in the cue letter set in 50 % of the trials. There were a total of 32 trials with alternating durations of short and long maintenance sessions. Each trial was followed by a rest phase lasting 5 seconds and the total duration of the task was 640 seconds. The participants performed the task at baseline (week 0), week 1, week 8 and upon study completion (Week 12). They were instructed to respond as accurately and quickly as possible and reaction time and accuracy was recorded for each trial (sample response file is available in Supplementary material 3; Table S3.1).

4.2.3 fMRI acquisition

Gradient echo echoplanar images (EPI) were used to acquire 320 T2*-weighted image volumes depicting BOLD contrast on a 3 Tesla GE Signa HDx MRI scanner at the Centre for Neuroimaging Sciences, King's College London. For each volume, 39 oblique axial slices parallel to the intercommissural plane were collected with the following parameters: slice thickness: 3 mm, slice gap: 3.3 mm, echo time (TE): 30 milliseconds, repetition time (TR): 2000 milliseconds, flip angle: 75°, field of view: 240 mm, and matrix size: 64 x64.

4.2.4 fMRI data analysis

Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK; Ashburner et al., 2012) was used to pre-process and analyse the task-related fMRI data using default settings. The images were realigned to correct for motion artefacts, spatially normalized to the Montreal Neurological Institute template, and smoothed using an 8mm full-width at half maximum Gaussian kernel filter. First-level analysis was performed using the general linear model, accounting for serial autocorrelations by applying an autoregressive model. The images corresponding to correct responses were used in the first level analysis to produce contrast images relevant to the main contrast of interest (encoding *vs* rest, short rehearsal *vs* rest, long rehearsal *vs* rest, short retrieval *vs* rest, long retrieval *vs* rest). Second-level analysis employed a random-effects model to examine the main effect of group (MDD *vs* HV) at baseline (week 0) and upon study completion (week 12), main effect of time (linear changes over weeks 0, 1, 8, 12) and the group x time interaction over the series of scans (linear effects).

Functional magnetic resonance imaging studies of working memory in depression that examined encoding and retrieval related effects separately have used less stringent thresholds than FWE corrected $p < 0.05$. For instance, Kelley & colleagues (2013) used a height threshold of $p < 0.001$ and extent threshold of 10 voxels to identify group differences (psychotic MDD, non-psychotic MDD and healthy volunteers). A recent study on episodic memory used a threshold of $p < 0.001$, corrected by Monte Carlo cluster simulation; cluster extent threshold of 43 voxels (Dietsche et al., 2014). Werner

et al. (2009) used a threshold of $p_{FDR} < 0.05$, while Fairhall et al. (2010) used height threshold at $p < 0.001$ and further corrected for multiple comparison at the cluster level.

In the present study, a voxel-wise threshold corrected for multiple comparisons ($p_{(FWE\ corrected)} < 0.05$) was used. As per recent recommendations (Woo et al., 2014), additional regions that survived a height threshold of p uncorrected < 0.001, and further corrected for multiple comparison at the cluster level (cluster level $p_{FWE} < 0.05$) as showing trends for significance were also reported. A voxel-level uncorrected $p < 0.001$ was used, as lower thresholds (ex. $p < 0.01$ or $p < 0.005$) are likely to lead to inaccurate FWE corrections (Woo et al., 2014).

To my knowledge, the only other study that examined antidepressant effects on encoding and retrieval separately has been a PET investigation by Bremner & colleagues (2007) that compared pre-treatment activations in MDD patients with changes after therapy, rather than examining changes over time. Therefore, in the present study, in addition to examining changes in brain activation across different time points (i.e. weeks 0,1, 8 and 12), a comparative analysis of baseline activations with changes after 12 weeks in MDD patients and in controls (paired t-test: week 0 *vs* week 12) was also performed. Additionally, a group by time interaction from the week 0 and week 12 scans was also done.

4.3 Results

4.3.1 Demographic results

Age, gender and IQ were not significantly different between patients and controls (all $p > 0.4$) (Table 4.1). Patients had significantly higher HAMD scores compared to patients ($p < 0.001$) which decreased following treatment ($p < 0.05$). Upon study completion, 18 patients met criteria for a clinical response to treatment defined by a minimum of 50% reduction in HAMD-17 score and 16 patients met criteria for clinical remission defined as a HAMD-17 score of 7 or less at the end of

treatment. Information on other clinical characteristics of patients such as illness onset, course, and duration, and treatment history were unavailable.

Table 4.1: Demographic and clinical characteristics

Characteristic	Patients with Depression (N=23)		Healthy Volunteers (N=22)	
	Mean	SD	Mean	SD
Age (years)	39.83	11.21	39.09	10.29
Full IQ	107.83	10.71	108.18	13.75
Verbal IQ	110.00	9.86	108.45	12.56
Performance IQ	103.17	14.43	106.36	15.31
HAMD (baseline)	21.96	2.85	0.32	1.09
HAMD (week 12)	6.87	4.62	0.59	1.22
HAMA (baseline)	20.74	5.39	*	*
HAMA (week 12)	7.52	4.41	0.50	1.01

* HAMA not done for healthy volunteers at baseline

4.3.2 Behavioural analysis

In the immediate (5 second) recall condition, there was a main effect of time ($F_{3, 126} = 13.83$, $p < 0.001$) with all participants responding faster with time. There were no main effects of group or group by time interaction effects. For accuracy, there were neither main effects of group or time nor any significant group by time interaction effect (Table 4.2).

In the delayed (15 second) recall condition, there was again a main effect of time ($F_{3, 126} = 12.90$, $p < 0.001$) as all participants made faster responses with time. There were no main effects of group or group by time interaction effects. For accuracy, there were neither main effects of group or time nor any significant group by time interaction effects (Table 4.2).

Table 4.2: Behavioural performance on the Sternberg task

	MDD Patients N=23	Healthy Controls N=22	*P* value
Baseline			
Immediate Recall			
Reaction Time	1577.64 (477.18)	1505.09 (281.75)	0.54
Percentage Accuracy	91.88 (7.96)	89.37 (9.50)	0.34
Delayed Recall			
Reaction Time	1635.48 (458.90)	1499.68 (368.51)	0.28
Percentage Accuracy	86.55 (9.18)	82.57 (10.00)	0.17
Week 12			
Immediate Recall			
Reaction Time	1368.12 (256.58)	1273.68 (166.42)	0.15
Percentage Accuracy	88.88 (12.33)	89.75 (8.73)	0.76
Delayed Recall			
Reaction Time	1374.88 (250.32)	1327.87 (183.85)	0.47
Percentage Accuracy	85.70 (17.27)	87.63 (10.52)	0.65

4.3.3 fMRI results

4.3.3.1 Encoding

4.3.3.1.1 Main effect of group

No significant main effects of group were observed at the baseline (week 0) or at the final scan (week 12).

4.3.3.1.2 Main effect of time

There were no significant linear effects of time over both groups, or within each group.

However, comparisons of baseline with final scan (week 0 *vs* week 12) showed main effect of time within each group. In MDD patients, there was a significant reduction in activation in the right

precentral gyrus (x = 24, y = -16, z = 50; k = 14, T = 6.50, $p_{(FWE\ corrected)}$ = 0.009) and left middle temporal gyrus (BA 37) (x = -38, y = -56, z = 10; k = 6, T = 6.34, $p_{(FWE\ corrected)}$ = 0.019) after 12 weeks compared with baseline scan. Additional regions showed a trend towards a decrease from weeks 0 to 12 in regions extending from the inferior frontal gyrus, through the middle and inferior temporal, to the inferior parietal regions (cluster level $p_{FWE} < 0.05$) (Table 4.3).

In healthy controls, there were no significant differences in regional brain activations from weeks 0 to 12. A trend towards a significant reduction in activation was found in a cluster comprising of the cerebellar vermis (x = 6, y = -58, z = -8; k = 1007, T = 5.02, cluster level $p_{FWE} < 0.001$) and additionally the left parahippocampal gyrus (subordinate peak: x = -18, y = -26, z = -16; T = 4.66, cluster level $p_{FWE} < 0.001$) and the right lingual gyrus (subordinate peak: x = 12, y = 32, z = -8; T = 4.65 cluster level $p_{FWE} < 0.001$) (Table 4.3).

4.3.3.1.3 Interaction effects

There were no significant linear group by time interaction effects, nor any significant group by time interaction effects from the week 0 and week 12 scans.

Table 4.3: Changes in regional brain activation in MDD patients and healthy controls at week 12 in comparison with baseline scans

Brain Region	MNI coordinates			Voxels	*T va*lue	*P* value
	x	y	z			
MDD Patients						
Right Precentral Gyrus	40	-18	52	564	4.04	0.005
Left Middle Temporal Gyrus	-42	-42	8	382	4.21	0.023
Left Inferior Temporal Gyrus	-60	-50	-10	557	5.95	0.005
	-60	-28	-14		5.77	0.005
Right Inferior Parietal Gyrus	54	-38	48	424	5.45	0.016
Right Inferior Frontal Gyrus	44	38	6	905	5.34	0.001
Right Middle Frontal Gyrus	34	52	4		4.82	0.001
Right Superior Frontal Gyrus	28	54	12		4.46	0.001
Left Supplementary Motor Area	-12	-20	50	643	5.21	0.003
Left Middle Cingulum	-14	0	46		4.56	0.003
Left Inferior Parietal Gyrus	-50	-48	44	461	4.88	0.011
Healthy Controls						
Vermis	6	-58	-8	1007	5.02	<0.001
Left Parahippocampal Gyrus	-18	-26	-16		4.66	<0.001
Right Lingual Gyrus	12	32	-8		4.65	<0.001

In all these regions, there was a reduction in activation at week 12 compared with baseline (all cluster $p_{FWE} < 0.05$)

*4.3.3.2 **Short rehearsal***

4.3.3.2.1 Main effect of group

There were no significant main effects of group at baseline or at the end of 12 weeks.

4.3.3.2.2 Main effect of time

No significant linear effects of time were observed over both groups, or within each group. In addition, the comparison of baseline with week 12 activations did not show a main effect of time in either of the groups.

4.3.3.2.3 Interaction effects

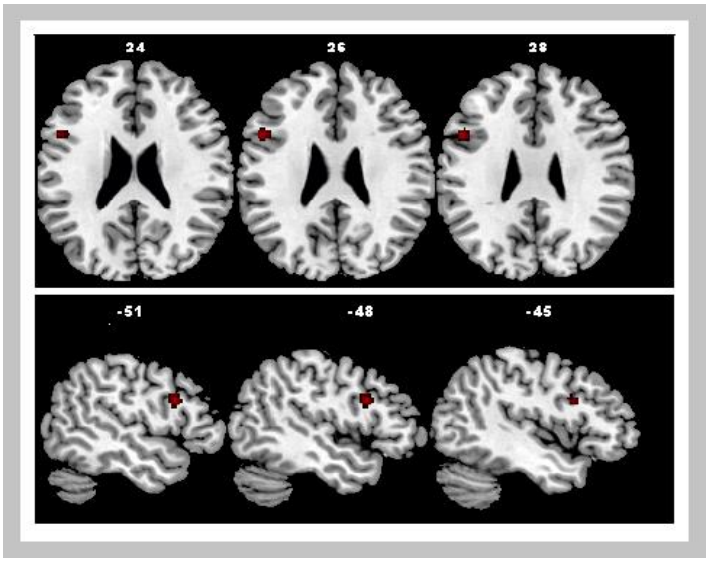
There were no significant linear group by time interaction effects, nor any significant group by time interaction effects from the week 0 and week 12 scans.

4.3.3.3 Long rehearsal

4.3.3.3.1 Main effect of group

No significant main effects of group were observed at baseline. At week 12, however, patients showed significant reduction compared to controls in the left inferior frontal gyrus (x = -48, y = 12, z = 26; k = 8, T = 5.08, $p_{(FWE\ corrected)} = 0.027$) (Figure 4.1).

Figure 4.1*:* Main effect of group at week 12 during long rehearsal



Patients showed significant reduction at week 12 in the left inferior frontal gyrus relative to controls ($p_{(FWE\ corrected)} < 0.05$)

4.3.3.3.2 Main effect of time

No linear effects of time were observed over both groups, or within each group. Comparison of baseline with week 12 scans did not reveal a main effect of time in patients. However, in controls, there was a trend for decrease at week 12 compared to baseline in the cerebellum (x = 8, y = -48, z = -12; k = 296, T = 4.82, cluster level $p_{FWE} = 0.047$) and cerebellar vermis (x = 4, y = -54, z = -8; k = 296, T = 4.94, cluster level $p_{FWE} = 0.047$).

4.3.3.3.3 Interaction effects

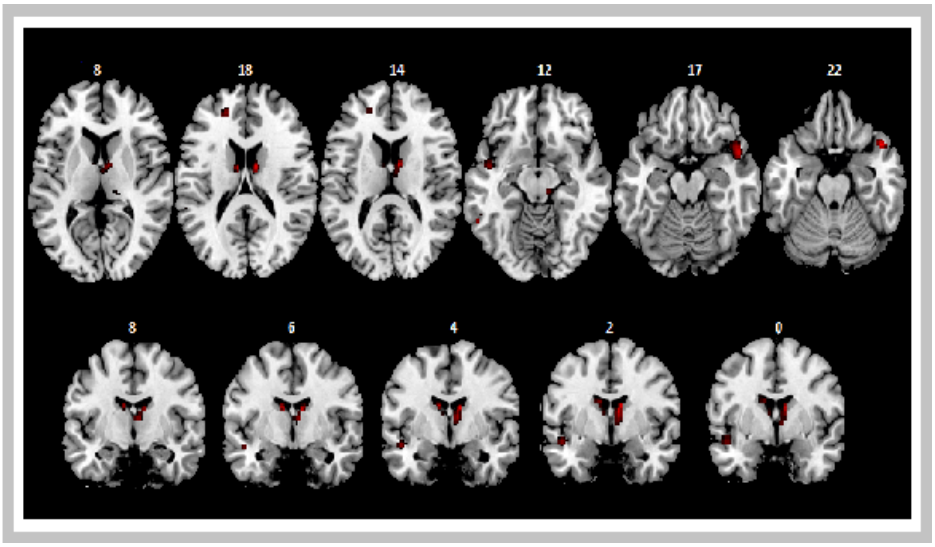
No significant linear effects of time over both groups, or within each group were observed. However, comparison of baseline with week 12 scans revealed a significant group by time interaction, such that there was a tendency for reductions in brain activations at week 12 relative to week 0 in controls in the bilateral caudate, left middle frontal gyrus, middle temporal gyrus, right mid cingulate gyrus, superior temporal pole and vermis, while no change was observed in patients (Table 4.4, Figure 4.2, Supplementary material 3, Table S3.2, Figure S3.1). There was also a group by time interaction in the left superior temporal gyrus, and this effect was due to patients showing a tendency for decreased activation in the final scan.

Table 4.4: Group by time interaction during long rehearsal

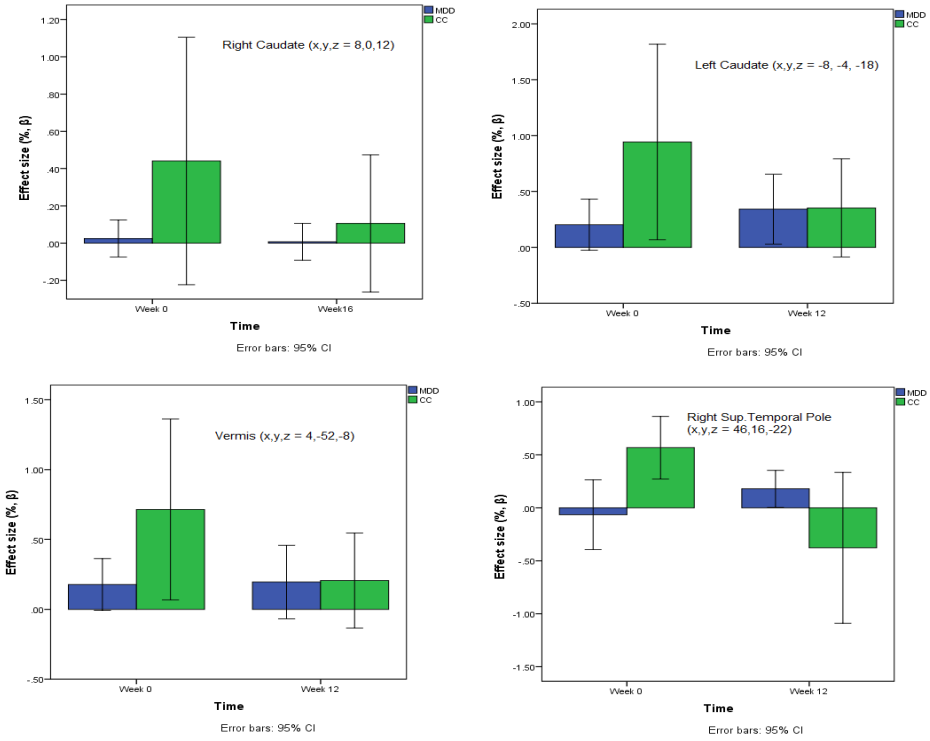
Brain Region	MNI coordinates			Voxels	*T va*lue	*P* value
	x	y	z			
Left Middle Frontal Gyrus	-20	46	16	50	5.35	0.001
Right Middle Cingulum	10	-26	34	40	5.31	0.001
Left Superior Temporal Gyrus	-58	-50	-12	28	5.19	0.002
	-58	-40	18	1	4.51	0.041
Right Superior Temporal Pole	46	16	-22	136	5.7	<0.001
	50	10	-18		5.48	0.001
Left Middle Temporal Gyrus	-48	-2	-14	66	5.15	0.003
Right Caudate	8	0	12	202	5.58	0.001
Left Caudate	-8	-4	18	83	5.42	0.001
Right Thalamus	12	-22	10	12	4.59	0.03
	16	-28	6		4.57	0.032
Vermis	4	-52	-8	40	5.06	0.004

Regions showing significant group by time interaction effect during long rehearsal (all $p_{(FWE\ corrected)} < 0.05$)

Figure 4.2: Group by time interaction during long rehearsal



(a) Regions showing group by time interaction effect ($p_{(FWE\ corrected)} < 0.05$)



(b) The graphs represent group by time interaction in the bilateral caudate, cerebellar vermis, and the right superior temporal pole. Effect sizes (β-weights) for the group by time interaction in the right caudate (x,y,z,= 8,0,12; $p_{(FWE\ corrected)} = 0.001$), left caudate (x,y,z, = -8,-4,18; $p_{(FWE\ corrected)} = 0.001$), vermis (x,y,z,= 4, -52, -8; $p_{(FWE\ corrected)} = 0.004$) and right superior temporal pole (x,y,z = 46,16, -22; $p_{(FWE\ corrected)} < 0.001$).

4.3.3.4 Short retrieval

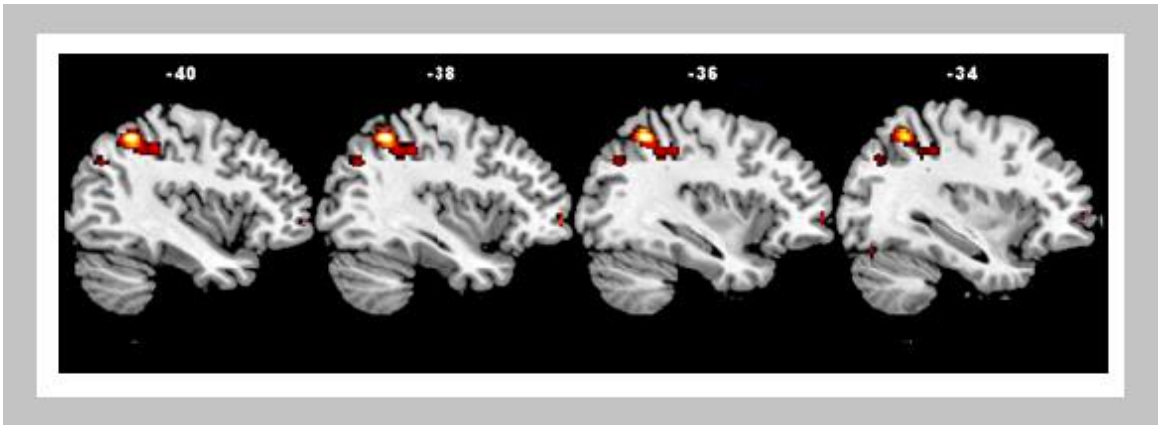
4.3.3.4.1 Main effect of group

There were no main effects of group neither at baseline, nor at week 12 following treatment with duloxetine.

4.3.3.4.2 Main effect of time

No significant linear effects of time over both groups, or within each group were observed. However, comparison of baseline scans with final week 12 scan revealed significant reduction in MDD patients in the left inferior parietal gyrus (x = -34, y = -32, z = 40; k = 1, t = 5.98, $p_{(FWE\ corrected)} = 0.038$) (Figure 4.3) and a trend for significance in the left postcentral gyrus (x = -32, y = -24, z = 46; k = 580, t=5.17, cluster level $p_{FWE} = 0.005$) at week 12 relative to baseline. In healthy controls, the right insula (x = 42, y = 6, z = -10; k = 1, t = 6.43, $p_{(FWE\ corrected)} = 0.035$) and the right inferior frontal gyrus (x = 50, y = 28, z = -4; k = 2, t = 6.75, $p_{(FWE\ corrected)} = 0.028$) showed significant reduction at week 12 compared to week 0 scans.

Figure 4.3: Pre-treatment *vs* post-treatment differences in MDD during short retrieval



Patients showed significant reduction in the left inferior parietal gyrus at week 12 relative to baseline ($p_{(FWE\ corrected)} < 0.05$)

4.3.3.4.3 Interaction effects

There were neither linear group by time interaction effects, nor any significant interaction effects from the week 0 and week 12 scans.

4.3.3.5 Long retrieval

4.3.3.5.1 Main effect of group

No significant main effects of group were observed at the baseline or at the final scan.

4.3.3.5.2 Main effect of time

No significant linear effects of time were observed for both groups or within each group over the series of scans. In MDD patients, there was a significant reduction at week 12 compared with baseline in the right precentral gyrus (x = 40, y = 4, z = 52; k = 3, t = 6.22, $p_{(FWE\ corrected)} = 0.029$) and the cerebellum (x = 32, y = -44, z = -32; k = 4, t = 6.17, $p_{(FWE\ corrected)} = 0.025$). Additional regions showed a trend towards a decrease from weeks 0 to 12 in regions extending from the inferior and superior frontal gyri, to the middle temporal and occipital regions (Table 4.5). No regions in controls showed a significant change at the final scan compared with baseline scan.

Table 4.5: Changes in regional brain activations during long retrieval in MDD patients at week 12 in comparison with baseline scans.

Brain Region	MNI coordinates			Voxels	*T va*lue	*P* value
	x	y	z			
Right Middle Temporal Gyrus	48	-58	14	3173	4.36	<0.001
Left Middle Occipital Gyrus	-34	-72	24	446	3.53	0.017
	-30	-72	32		3.35	0.017
Left Mid Cingulum	-8	-2	48	1401	3.92	<0.001
Left Superior Frontal Gyrus	-22	-8	54		3.88	<0.001
Left Inferior Frontal Gyrus	-34	-36	44		3.79	<0.001

In all these regions, patients showed reduction in activation after 12 weeks of treatment compared to baseline (all cluster $p_{FWE} < 0.05$)

4.3.3.5.3 Interaction effects

There were no significant linear group by time interaction effects, or any significant group by time interaction effects from the week 0 and week 12 scans.

4.4 Discussion

The study examined the behavioural responses and the neural correlates of working memory in acutely depressed MDD patients and following 12 weeks of treatment with a dual acting serotonin norepinephrine reuptake inhibitor, Duloxetine.

4.4.1 Behavioural results

The behavioural responses did not reveal any significant difference between the groups in working memory, consistent with findings from previous studies using the n-back (Harvey et al., 2005; Rose et al., 2006; Matsuo et al., 2007) and Sternberg (Siegle et al., 2002) tasks. Moreover, a study that examined various cognitive functions in MDD patients revealed no marked decline in patients during immediate, implicit, semantic, and recognition memory (Ilsley et al., 1995). In fact, a meta-analysis of first-episode MDD patients did not find significant impairments in verbal memory in patients relative to healthy controls (effect size =0.13, p=0.40) (Lee et al., 2012). Memory impairments may be more likely in severely depressed patients who need hospitalization (ex. Sternberg et al., 1976), or those with comorbid illnesses such as anxiety (Kizilbash et al., 2002; DeLuca et al., 2005). The sample used in this study comprises patients with a less severe form of depression without psychiatric comorbidity, and are representative of patients found in the community. Memory impairments in depression are also more evident in response to cognitively challenging tasks. For instance, performance inaccuracies were more likely in MDD patients when the memory load on the working memory task was high (ex. Vasic et al., 2009), a distractor element was introduced in the task (ex. Porter et al., 2003), or when the task required recognition of a previously encoded stimuli from a group of very similar stimuli after a delayed period (ex. Porter et al., 2003). It is likely that MDD patients in the current study sample may show impairments in working memory if they are assigned a more cognitively challenging task.

4.4.2 fMRI results

4.4.2.1 Encoding

The neural correlates did not reveal any significant group differences at baseline or upon study completion, any linear group by time interaction effects or any other interaction effects from the week 0 and week 12 scans. However, MDD patients showed a significant reduction in activations in the precentral gyrus and the middle temporal gyrus at week 12 relative to baseline scans. Additionally, the right prefrontal regions, left inferior temporal, cingulate regions and the bilateral inferior parietal gyrus showed a trend for reduction after 12 weeks. The precentral gyrus is associated with motor control (Sanes et al., 1995) and engaged by both working memory and visuospatial attention tasks (LaBar et al., 1999). In healthy controls, precentral gyrus (specifically Brodmann area 6) activations are seen in response to both non-verbal and verbal encoding (Kelley et al., 1998; Wagner et al., 1998). The middle temporal gyrus is also involved in the encoding of words (Anderson et al., 2000; Jackson & Schacter, 2004) and activation in this region during encoding is associated with successful recognition (Jackson & Schacter, 2004). Comparison of MDD patients and controls in tasks of working memory showed increased activations in the precentral gyrus (Harvey et al., 2005) and decreased activations in the middle temporal gyrus (Werner et al., 2009) in patients. In the present study, there were no significant baseline differences in neural activations between the groups. However, the results of the present study are consistent with previous PET findings that showed reductions in MDD patients after treatment in the middle/superior frontal, inferior temporal gyrus, and parietal regions during encoding (Bremner et al., 2007). Although the findings from this study only showed a trend for significance in these regions, variation in the functional imaging technique employed and the use of what may be perceived as a more liberal threshold ($p < 0.005$ with extent threshold of 40 voxels) in Bremner et al. (2007) may have contributed to some of the differences in effect size. The decreased engagement of the prefrontal and parietal areas after duloxetine treatment in MDD patients in the present study may indicate less reliance on these regions during working memory after treatment.

*4.4.2.2 **Rehearsal***

The neural correlates did not reveal any group by time interaction effects or main effects of group or time for the short rehearsal phase. However, a significant interaction effect during the long rehearsal phase in the left superior temporal gyrus was observed, and this effect was due to patients showing a tendency for decreased activation with time. Additional group by time interaction effects in a network of regions extending from the middle frontal, caudate/thalamus, mid cingulate, down to the superior temporal pole and the cerebellar vermis were also observed. In healthy controls, there was a tendency for reductions in activations in these regions from week 0 to week 12, while no change was observed in patients. The neural correlates of n-back working memory in healthy controls constitute a network of regions comprising the dorsal cingulate, medial and inferior frontal regions, premotor cortex, frontal poles and posterior parietal regions (Owen et al., 2005). The present study found significant group by time interaction within this network. Walsh et al. (2007) also found a group by time interaction in the caudate and thalamus with fluoxetine in response to a verbal working memory task, whereby controls showed a decrease in activation with time, while the opposite effect was seen in patients. In the current study, tendency for decreased activations in controls in the follow up scan is perhaps indicative of less recruitment of these regions with increased familiarity with the task, while no change in activation in patients may reflect persistent recruitment of regions associated with working memory to maintain task performance.

The results in the present study must be considered preliminary and further investigations with a larger sample size are required to confirm obtained findings. Previous longitudinal studies in depression have predominantly used affective stimuli (see meta-analysis Delaveau et al., 2011; Ma, 2015) and only few imaging studies have examined treatment effects on the neural correlates of working memory (ex. Bremner et al., 2007; Walsh et al., 2007). These studies have either not examined the effects of treatment on maintenance related activations (Bremner et al., 2007) or used the n-back task that did not permit delineation of maintenance related brain activations from encoding or retrieval related activations (Walsh et al., 2007).

In addition to examining changes in regional brain activations in MDD patients with treatment, neural changes in healthy volunteers were also examined to account for effects of time or effects of repeated scans. In healthy controls, both the encoding and the long maintenance phase showed a trend towards reduction in the cerebellum at week 12 compared with baseline trial. Cerebellum is frequently engaged by working memory tasks, learning and reading paradigms, as well as other tasks of executive function (Stoodley, 2012). In healthy controls, practice induced deactivation in the cerebellum is evident in tasks of visual attention (Tomasi et al., 2004) verbal production (Peterson et al., 1998) and non-motor learning (Raichle et al., 1994). Previous research has shown main effects of time in the cerebellum, with decreased activation in MDD patients and controls in response to sad (Fu et al., 2004, Fu et al., 2008a) and happy (Fu et al., 2007) facial processing, and verbal working memory (Walsh et al., 2007). The reduction in cerebellum activations after 12 weeks in the present study perhaps reflects effects of repeated scanning in healthy volunteers.

4.4.2.3 Retrieval

The findings did not reveal any significant linear group by time interaction effects or any group by time interaction effects from the week 0 and week 12 scans during the short and long retrieval phases. The main effect of group also failed to showed significant differences either at baseline or upon study completion during the retrieval phases.

Retrieval related activations are usually associated with ventrolateral prefrontal regions (Narayanan et al., 2005; meta-analysis: Cona et al., 2015). However, brain activation specifically associated with retrieval in MDD patients has been examined in very few fMRI studies (ex. Werner et al., 2009; Kelley et al., 2013; Dietsche et al., 2014). Findings from these studies however have been inconsistent, with evidence of retrieval related increases in the inferior frontal gyrus (Dietsche et al., 2014), and in superior frontal gyrus (Werner et al., 2009), as well as decreases in the anterior cingulate gyrus (Werner et al., 2009; Kelley et al., 2013) in MDD patients relative to controls. The differences in the brain activations may reflect variations in the fMRI paradigms used in these studies. For instance, Dietsche et al. (2014) and Werner et al. (2009) presented items as faces. The former study used neutral faces, while the latter used a face-profession task that was not limited to neural

faces. Kelley et al. (2013) on the other hand used a verbal declarative memory task, although different from the task used here. In this study, each trial was associated with an encoding, rehearsal and retrieval stage, unlike Kelley et al. (2013) where encoding and retrieval tasks were individual scans, separated by a five minute scan to minimise the possibility of rehearsal (Kelley et al., 2013).

The neural effects of antidepressants on retrieval or recognition have been previously examined in healthy volunteers (ex. Miskowiak et al., 2007; Norbury et al., 2008; Tendolkar et al., 2011) and less extensively in MDD patients (ex. Bremner et al., 2007). Decreased activations in the precentral gryus and cerebellum following treatment were observed in the present study, and additional trends in the middle temporal gyrus, inferior and superior frontal gyrus and the mid cingulate gyrus during the long retrieval stage. Interestingly, decreased baseline activations in all these regions during verbal working memory were associated with better clinical response (Walsh et al., 2007). Decreases in mid cingulate activations reported in this study were also evident in healthy controls after seven days of treatment with reboxetine (Norbury et al., 2008). Acute or short term antidepressant treatment in healthy controls were also associated with increases in the amygdala during mood-incongruent memory retrieval (Tendolkar et al., 2011) as well as decreases in the fronto-parietal network during successful recognition of positive personality-trait words (Miskowiak et al., 2007; Norbury et al., 2008). In MDD patients, consistent with results from the present study, PET investigations found retrieval related decreases after SSRI treatment in the superior frontal gyrus (Bremner et al., 2007). There were also some inconsistencies, for instance, the inferior frontal gyrus showed decreases with treatment in the present study, while the opposite effect was observed in Bremner et al. (2007). It is important note that unlike the present study, previous studies (Bremner et al., 2007; Miskowiak et al., 2007; Norbury et al., 2008; Tendolkar et al., 2011) used affective paradigms, and processing of affective material may be associated with distinct neural correlates (Bourke et al., 2010). Moreover, Tendolkar et al. (2011) used an initial height threshold of $p < 0.005$ and according to a recent study, lowering thresholds beyond $p < 0.001$, may lead to incorrect FWER corrections and are undesirable in neuroimaging research (Woo et al., 2014). Future investigations on the effects of antidepressants on the neural correlates of working memory are required to confirm present findings.

4.4.3 Limitations

Limitations of the present study include the small sample size, which may have led to insufficient power to detect all group differences at the neural level. Also, the high response rate in this study limited the power to detect differences between treatment responders and patients with a more treatment resistant form of depression, which may be associated with distinct neural correlates (Fu et al., 2008a). Finally, the absence of a treatment group receiving placebo limits our attribution of effects to the antidepressant medication as opposed to changes associated with clinical improvement, although the potential effects of time were accounted for by having HV participants undergo scans at the same time points as MDD patients.

In summary, the functional neuroimaging correlates failed to show any baseline group differences or group by time interaction effects during the encoding and retrieval phases of working memory. There was however a significant group by time interaction during the long rehearsal phase, such that there was a tendency for reductions in brain activations at week 12 relative to week 0 in controls in a network of brain areas extending from the prefrontal, to the cingulate, temporal and cerebellar regions, while no change was observed in patients. The tendency for decreased activations in controls in the follow up scan is perhaps indicative of less recruitment of these regions with increased familiarity with the task, while no change in activation in patients may reflect persistent recruitment of regions associated with working memory to maintain task performance. Further placebo-controlled investigations with larger sample are required to confirm the present findings and delineate antidepressant effects from changes associated with clinical improvements.

5 Diagnostic and prognostic potential of structural neuroimaging data in major depressive disorder

5.1 Introduction

At the present time, the diagnosis of MDD is determined by clinical signs and symptoms, and there are no biological measures for the diagnosis. Neuroimaging offers the potential to develop biomarkers for diagnosis as well as in the prediction of clinical response and course of illness (Fu & Costafreda, 2013).

Structural neuroimaging studies of MDD have revealed widespread cortico-limbic regional deficits in grey matter (reviewed in: Atkinson et al., 2014) as well as in white matter (Korgaonkar et al., 2011; Cole et al., 2012). There is evidence that some regional atrophy in the hippocampus may already be present in the first episode of MDD (Cole et al., 2011) and may worsen with recurrent episodes, in particular in patients with a more treatment-resistant form of MDD (MacQueen & Frodl, 2011), although an earlier study found no significant difference in hippocampal volume between controls and patients with early onset depression (Lloyd et al., 2004). In order for a potential clinical application, it is important that biological markers be established with high predictive accuracy at the individual level. Methods of analysis, for instance, those based on machine learning algorithms such as Support Vector Machine (SVM) provide an opportunity to develop classification measures which may be applied to an individual subject (Fu et al., 2008b).

Multivariate pattern analysis using SVM has demonstrated the potential of structural neuroanatomy in classifying MDD. For example, one of the earliest studies performed on 37 MDD patients and an equal number of healthy controls revealed that grey matter volume could distinguish acutely depressed patients from healthy controls with an accuracy of 67.6% (Costafreda et al., 2009b). Since then, different pattern classification techniques have investigated the predictive power of grey matter volume in the diagnosis of MDD (Table 5.1) using first episode (Qiu et al., 2014) treatment-naïve MDD patients (Liu et al., 2012; Qiu et al., 2014), medication free MDD patients in an acute depressive episode (Costafreda et al., 2009b), MDD patients on antidepressant medication (Mwangi et al., 2012) and psychotic MDD patients (Serpa et al., 2014). Furthermore, as MDD patients show a substantial variation in how they respond to treatment, and because non-response to pharmacotherapy

may represent a more chronic form of the disorder, predictors of illness have been studied in treatment sensitive and treatment resistant patients separately. For instance, Gong & colleagues (2011) found that grey matter volume was better at discriminating treatment sensitive (76.09 %, $p < 0.001$) when compared to treatment resistant (67.39 %, $p < 0.01$) MDD patients from healthy volunteers, whilst a newer study based on a slightly smaller size revealed similar accuracy rates (82.4 % and 85.7 % respectively) (Liu et al., 2012). Grey matter regions of the frontal temporal, parietal, occipital regions (Costafreda et al., 2009b; Gong et al., 2011; Liu et al., 2012), including the superior frontal, angular and middle temporal gyri (Gong et al., 2011; Liu et al., 2012), and cerebellum (Costafreda et al., 2009b; Liu et al., 2012), have consistently showed potential for diagnosis prediction. Although studies typically investigated regional volumetric features in MDD patients, geometric features, such as Jacobian metric distortion also showed potential for diagnosis (Qiu et al., 2014).

Building on evidence from structural MRI (Janssen et al., 2007; Amico et al., 2011) and Diffusor Tensor Imaging (DTI) (Li et al., 2007; Kieseppa et al., 2010; Korgaonkar et al., 2011; Cole et al., 2012) data suggesting white matter abnormalities in acutely depressed patients, studies have sought to investigate the predictive potential of white matter volume in the diagnosis of MDD (Table 5.1). It has been proposed that the structural and functional cortical grey matter changes in depression may be communicated through underlying subcortical white matter changes (Korgaonkar et al., 2011). Alterations in white matter integrity is evident in depression (Cole et al., 2012), including in the first episode of MDD (Zhu et al., 2011) and in adolescents with familial risk, even before they manifest any clinical symptoms of the illness (Huang et al., 2011). White matter distinguished treatment sensitive patients from healthy controls with an accuracy of 84.65 % (Gong et al., 2011) and 91.2 % (Liu et al., 2012), which was better than that with grey matter (76.09 % and 82.4 % respectively). These findings outline the underlying neural mechanisms associated with the pathophysiology of depression and suggest the need to investigate multiple neuroanatomical features in classification.

In addition, investigation of biological markers of clinical response in MDD has been of particular interest (Table 5.2) as they help optimize treatment strategies at an early stage especially for those patients who are less likely to benefit from the usual first line treatment options. Using neuroimaging

measures, it has been possible to identify markers of prognosis even before the initiation of treatment or early in the course of treatment (Fu et al., 2013). Notably, grey matter density predicted response to antidepressants (Costafreda et al., 2009b: 88.9 %; Gong et al., 2011: 69.57 %; Liu et al., 2012: 82.9 %) better than to cognitive behavioural therapy (Costafreda et al., 2009b: non-significant finding). Additionally, a study that employed feature selection and feature based morphometry to the classification algorithm obtained a prognostic accuracy as high as 90 % with antidepressants (Mwangi et al., 2012). One of the most widely replicated biomarker of clinical response is the anterior cingulate, which has been reported across different structural (Costafreda et al., 2009b; Liu et al., 2012) and functional (see meta-analysis: Fu et al., 2013) neuroimaging studies.

However, these studies that examined the potential of structural data to predict diagnosis and prognosis have several limitations: homogenous ethnic group (Chinese: Gong et al., 2011; Liu et al., 2012; Qiu et al., 2014; Caucasian: Costafreda et al., 2009b; Mwangi et al., 2012) limiting the generalizability of the findings to other races; restriction to treatment-naïve MDD patients (Liu et al., 2012; Qiu et al., 2014) reducing the translational value of the results in patients with a more chronic form of the disorder, inclusion of medicated MDD patients (Mwangi et al., 2012) eliciting confounding drug effects on brain structure, heterogeneous antidepressant treatment (Gong et al.,2011; Liu et al., 2012) and inclusion of grey matter only (Costafreda et al., 2009b). These limitations have been addressed in the present study by including medication-free patients of white, Asian and African descent, incorporating both first episode MDD patients as well as those at a later stage of the disorder, administering a stable dose of a single drug duloxetine belonging to the SNRI class and investigating the potential of both grey and white matter in predicting diagnosis and prognosis.

The present study examined whether MDD patients could be distinguished from healthy controls based on their structural neuroanatomy using SVM. In addition to examining grey and white matter volumes individually, a combined analysis of both features was also performed to examine its influence on accuracy rates. In line with previous findings (Costafreda et al., 2009b; Gong et al., 2011; Liu et al., 2012), it is hypothesized the structural correlates of prefrontal, parietal and temporo-

occipital regions to show significant predictive power for diagnosis. Consistent with the literature, it is also expected that white matter would show higher predictive accuracy than grey matter.

The potential of grey matter and white matter to predict clinical remission with duloxetine was also investigated. To my knowledge, this is the first study that has examined the potential of structural data to predict prognosis with duloxetine, as previous studies used SSRIs (Costafreda et al., 2009b) and non-specific antidepressants (Gong et al., 2011; Liu et al., 2012). It is expected that the anterior cingulate would show high predictive accuracy for clinical outcome at the level of the individual.

Table 5.1: Studies investigating prognostic potential in MDD using structural MRI data

Author	Year	MRI	Healthy Control N(Male)	Healthy Control Age	Patients N(Male)	Patients Age	Diagnosis	Severity (HAMD)	Medication	Comparison	Classifier	Feature	Accuracy	Sensitivity	Specificity	*P* value
Costafreda	2009	1.5 T	37(9)	42.8(6.7)	37(9)	43.2(8.8)	MDD	20.6(2.2)	Med free	MDD *vs* HV	SVM	GM	67.6	64.9	70.3	0.027
Gong	2011	3 T	23(12)	38.2	23(10)	39.2(12.9)	MDD	24.2(3.8)	Med naïve	MDD *vs* HV	SVM	GM	76.1	69.6	82.6	<0.001
												WM	84.7	73.9	95.7	<0.001
												GM+WM	76.1	73.9	78.3	<0.001
					23(14)	40.4(12.6)	TRD	23.5(5.4)	Med naïve	TRD *vs* HV		GM	67.4	65.2	69.6	0.01
												WM	58.7	60.9	56.5	0.13
												GM+WM	65.2	65.2	65.2	0.02
Liu	2012	1.5 T	17(10)	24.2(4.4)	17(10)	26.7(7.7)	MDD	25.6(6.3)	Med naïve	MDD *vs* HV	Searchlight-PCA-SVM	GM	82.4	-	-	-
												WM	91.2	-	-	-
											RFE-SVM	GM	70.6	-	-	-
												WM	76.5	-	-	-
											LLE- C Means	GM	76.5	-	-	-
												WM	88.2	-	-	-
											LLE-SVM	GM	82.4	-	-	-
												WM	88.2	-	-	-
					18(11)	27.4(7.7)	TRD	23.9(3.7)	*On meds	TRD *vs* HV	Searchlight-PCA-SVM	GM	85.7	-	-	-
												WM	85.7	-	-	-
											RFE-SVM	GM	77.1	-	-	-
												WM	85.7	-	-	-
											LLE- C Means	GM	77.1	-	-	-
												WM	85.7	-	-	-
											LLE-SVM	GM	77.1	-	-	-
												WM	85.7	-	-	-
Mwangi	2012	1.5 T	18(7)	40.6(10.3)	15(6)	46.1(12.5)	TRD	23.2(4.3)	On meds	TRD *vs* HV	VBM-FBM-SVM	GM	90.3	93.3	87.5	**1X10^{-7}
			14(7)	43.0(13.2)	15(5)	44.7(10.0)	TRD	27.9(5.8)			RVM	GM	87.1	86.7	87.5	**1X10^{-7}
*Kipli	2013	-	-	-	-	-	-	-	-	-	SVM-EM	GM+WM+CSF	85.3	-	-	-
											IG-Rand Tree		85.3	-	-	-
											SVM-Kmeans		82.3	-	-	-
Serpa	2014	1.5 T	38(8)	29.7(7.9)	19(4)	29.1(8.3)	pMDD	***16.1	*On meds	pMDD *vs* HV	SVM	GM+WM+Ventricles	59.6	31.6	73.7	-
Qiu	2014	3 T	32(23)	35.0(11.2)	32(23)	34.9(11.1)	MDD	24.3(5.1)	Med naïve	MDD *vs* HV	SVM	Cortical Thickness	69	66	72	0.002
												Volume	66	63	69	0.005
												Plial Area	69	69	69	0.001
												Curvature	48	47	50	0.63
												Area	59	66	53	0.10
												Sulcal Depth	58	56	59	0.12
												Jacob Met. Distort	67	63	72	0.002
												++All Parameters	69	69	69	0.002

Abbreviations: (Only those not mentioned elsewhere in the thesis are expanded here) TRD: Treatment Resistant Depression; pMDD: Psychotic MDD; PCA: Principle Component Analysis; RFE: Recursive Feature Elimination; LLE: Locally Linear Embedding; RVM: Relevance Vector Machine; FBM: Feature Based Morphometry; EM: Classification via clustering EM; K Means: Simple K Means Classification via Clustering; IG: Information Gain. Jacob. Met. Distort.: Jacobian Metric Distortion. Age in years with standard deviation (SD) in parenthesis; N: number of participants with number of males in parenthesis. HAMD: Mean values with SD in parenthesis. *Some of the patients were medication free. **chi square p value. *** 31 item HAMD. *Kipli (2014) - 82.3% accuracy also obtained with other classifiers: IG:-J48, IG-RandomForest, SVM-KMean, SVM-RandomForest, ReliefF- RandomTree, All-Naïve bayes; ++All Parameters: all the morphometric parameters of both hemispheres within a single model were integrated.

Table 5.2: Studies investigating prognostic potential in MDD using structural MRI data

Author	Year	MRI	Patients							Treatment	Analysis	Classifier	Feature	Acc.	Sensitivity	Specificity	*p
			Outcome	N (Male)	Age	Severity	Outcome	N (Male)	Age	Severity								
Costafreda	2009	1.5 T	Remit	9(2)	44.2(10.3)	20.2(1.7)	Non- Remit	9(2)	44.1(6)	22.0(2.8)	Fluoxetine	Remit vs Non-Remit	SVM	GM	88.9	88.9	88.9	0.01
				6(2)	41.2(11.7)	20.7(2.0)		6(2)	42.7(6.6)	20.8(1.9)	CBT				nil	nil	nil	nil
Gong	2011	3 T	TSD	23(9)	39.2(12.9)	24.2(3.8)	TRD	23(14)	40.4(12.6)	23.5(5.4)	Multiple AD	TRD vs TSD	SVM	GM	69.6	69.6	69.6	0.01
														WM	65.2	56.5	73.91	0.02
														GM+ WM	69.6	69.6	69.6	0.01
Nouretdinov	2011	1.5 T	Remit	9(2)	44.2(10.3)	20.2(1.7)	Non- Remit	9(2)	44.1(6)	22.0(2.8)	Fluoxetine	Remit vs Non-Remit	TCP-t test-SVM	GM	77.8	77.8	77.8	-
													TCP-t test-filter		83.3	77.8	88.9	-
Liu	2012	1.5 T	TSD	17(10)	26.7(7.7)	25.6(6.3)	TRD	18(11)	27.4(7.7)	23.9(3.7)	Multiple AD	TRD vs TSD	SLight-PCA-SVM	GM	82.9	-	-	-
														WM	82.9	-	-	-
													RFE- Linear SVM	GM	77.1	-	-	-
														WM	82.9	-	-	-
													LLE-C Means	GM	77.1	-	-	-
														WM	65.7	-	-	-
													LLE-SVM	GM	80	-	-	-
														WM	77.1	-	-	-

Abbreviations: CBT: Cognitive Behaviour Therapy, ADs: Antidepressants, PCA: Principle Component Analysis, TCP: Transductive Conformal Predictor, Slight: Searchlight, LLE: Locally Linear Embedding, RFE: Recursive Feature Elimination, Acc.: Accuracy. *p represents p value round to two decimal place

5.2 Method

5.2.1 Participants

This study was funded by Eli Lilly and company, and approved by the Cambridgeshire 4 Research Ethics Committee. The study was conducted in conformity with the Declaration of Helsinki and its amendments.

The structural data was obtained from the same participants who took part in the longitudinal study that examined the effects of duloxetine on the functional correlates of depression (Chapters 3 & 4). All participants were right-handed adults who provided informed written consent (Fu et al., 2015). Participants were patients with major depressive disorder (n = 23) and healthy controls (n = 20) matched for age, gender and IQ (all $p > 0.3$) (Table 5.3). A diagnosis of MDD, single or repeated episode without psychotic features, was made as defined by Diagnostic Statistical Manual of Mental Disorders, Fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000) and assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV; First et al., 2012) without any comorbid disorders. All MDD patients had a minimum score of 18 on the 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) at the time of study entry and were free of antidepressant medication for a minimum of 4 weeks before start of the study (or 6 weeks for fluoxetine). Medical reports were acquired from the General Practitioners for all participants and they were extensively examined to obtain information on antidepressant use, medication history, concomitant medications, and previous history of psychiatric illness other than major depressive disorder, previous treatment for depression or other psychiatric conditions, and any other medical or physical condition that met exclusion criteria for the study. Healthy controls had no history of psychiatric disorders, interviewed with SCID-IV (First et al., 2012), and had a HAMD score of ≤ 7. MDD patients received treatment with the serotonin norepinephrine reuptake inhibitor class of antidepressant, duloxetine, following the initial neuroimaging scan starting at a dosage of 60 mg once daily for 12 weeks. As expected, patients had significantly higher HAMD

scores at baseline ($p < 0.001$), which improved following treatment ($p < 0.001$). Upon study completion, 18 MDD patients met criteria for a clinical response, as defined by > 50 % reduction in HAMD score, and 16 MDD patients met criteria for clinical remission, as defined by a HAMD-17 score of ≤ 7. Information on other clinical characteristics of patients such as illness onset, course, and duration, and treatment history were unavailable.

Table 5.3: Demographic and clinical characteristics

	MDD Patients	Healthy Controls	*P* value
Number	23	20	
Age	39.8 (11.2)	38.8 (9.9)	0.84
Male, n (%)	13 (56.5)	12 (60.0)	0.82
Baseline			
HAMD	22.0 (2.9)	0.5 (1.1)	<0.001
HAMA	20.7 (5.4)	n/a	
Week 12			
HAMD	6.9 (4.6)	0.6 (1.3)	<0.001
HAMA	7.5 (4.4)	0.6 (1.1)	<0.001
Full IQ	107.8 (10.7)	109.2 (14.6)	0.63
Performance IQ	103.2 (14.4)	107.9 (15.2)	0.30
Verbal IQ	110.0 (9.9)	109.8 (12.4)	0.95

Mean values and standard deviations are presented in parentheses. Age is presented in years.

Neuroimaging scans were acquired at baseline (week 0), weeks 1, 8 and upon study completion (week 12). Baseline scans were obtained from 29 MDD patients and 22 healthy controls and structural neuroimaging data are presented from the baseline scan. Data from 2 healthy volunteers had to be excluded due to excessive moment during the structural scan. Since, the use of SVM requires approximately equal number of participants, data from the participants who completed the study (i.e. 23 MDD and 20 HV) were used. Of these, 18 patients responded to treatment and 16 patients achieved full clinical remission at the end of treatment.

5.2.2 Data acquisition

Structural MRI scans were acquired on a 3.0 T GE SIGNA HDx (Milwaukee, USA) at King's College London. A structural image was acquired at each session: Magnetization Prepared Gradient Echo, resolution $1mm^3$, acquisition parameters: TE: 30 ms, flip angle: 90°, slice thickness: 3 mm, interslice gap: 0.3 mm, number of slices, matrix size: 64 x 64.

5.2.3 Image preprocessing

Pre-processing of the structural MRI T1 weight images included bias correction, skull stripping and tissue segmentation. Bias correction was performed using N41TK, which is an improved MNI_N3 bias correction software package available at: http://www.insight-journal.org/browse/publication/640package. Skull stripping was completed using Multi- Atlas Skull Stripping software (MASS, version 1.0), which is based on a multi-atlas registration framework and uses a set of templates from the study data set which best represent the anatomical variations (Doshi et al., 2013). The images were then segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the automated algorithm Multiplicative Intrinsic Component Optimization (MICO) (Li et al., 2014). The quality of the processed images was ensured by automated quality control measures and manual review.

Spatial registration of all the skull stripped images to the Jakob template was performed using the Deformable Registration via Attribute Matching and Mutual-saliencing Matching registration package (DRAMMS, version 1.1.0) (Ou et al., 2011). The deformation field from the resulting registration was used to obtain the Regional Analysis of Volumes Examined in Normalized Space (RAVENS) maps or regional volumetric maps for grey matter, white matter and cerebrospinal fluid. The maps were corrected for individual intracranial volume, down sampled to 2x2x2 mm, and smoothed using an 8mm full width at half maximum (FWHM) Gaussian filter.

5.2.4 Analysis of structural neuroanatomy: grey and white matter

Regional differences in grey and white matter between MDD patients and healthy controls were performed using the Optimally Discriminative Voxel Based Analysis (ODVBA, version 2.0) software package (Zhang & Davatzikos, 2011) using the RAVENS maps. In the ODVBA approach, the optimal size and shape of the spatial smoothing is estimated from the data set prior to the statistical analysis. ODVBA applies a form of matched filtering using machine learning techniques to optimally detect group differences. It uses a spatially adaptive scheme which is designed to detect group differences with maximum sensitivity (Zhang & Davatzikos, 2011) and to improve identification of group differences (Zhang & Davatzikos, 2013). Finally, the statistical significances are obtained by using permutation tests. In the present study, 2,000 permutations were used to derive the significances, and significance was assigned as p (uncorrected) < 0.001 due to the relatively small sample size. ODVBA has shown greater sensitivity to detect subtle structural abnormities and improved delineation of the region of abnormality as compared to conventional GLM methods (Zhang & Davatzikos, 2011; 2013) in numerous clinical studies (Chaim et al., 2014; Erus et al., 2015; Zhang et al., 2015).

5.2.5 Classification using support vector machine

The grey matter and white matter RAVENS maps were concatenated into a single feature vector for each subject. Classification was then performed using SVM (Vapnik & Cortes, 1995), a multivariate classification technique that can optimally use high dimensional information such as neuroimaging data (Fu et al., 2008b; Costafreda et al., 2009b). SVM identifies the optimal linear decision boundary, or hyperplane, that has the maximum margin separating the two training groups (in the present study: MDD patients and healthy controls; MDD remission and MDD non-remission). SVM treats individual images as points located in high dimensional space. In SVM, both the hyperplane as well as the margin are important in classification accuracy, and usually the wider the margin the better the classification accuracy (Gaonkar et al., 2015).

SVM also extracts weight vectors as images, known as SVM discrimination maps, which represent the direction in which the two groups differs the most; however, these maps do not specify the statistical significance associated with the voxel or region (Gaonkar & Davatzikos, 2013). In order to sufficiently explore the small p-value regime, it would be necessary to perform millions of permutation tests which require tremendous computational overhead in terms of data storage and time. Instead, the necessary p-values may be estimated using analytical permutation testing (Gaonkar & Davatzikos, 2013). An advanced version of the approximation which accounted for the SVM margins in addition to the SVM weights was used in this study (Gaonkar et al., 2015). The SVM analysis was performed using five-fold cross validation strategy.

The classification scores derived from the SVM analysis was evaluated using a receiver operating characteristic (ROC) curve to illustrate the diagnostic accuracy of the classifier. The ROC curve was obtained by plotting the true positive rates (y axis: corresponding to sensitivity values) against false positive rates (x axis: corresponding to 1-specificity values) using individual z scores generated by the SVM classifier (Metz et al., 2006). The area under the curve (AUC) was calculated from the ROC curve, which is a measure of the discriminative power of the classifier and is independent of the chosen p value or sample size.

5.2.6 Classification using COMPARE analysis

The grey and white matter RAVENS maps were also analysed using the SVM-based classification technique Classification of Morphological Patterns using Adaptive Regional Elements (COMPARE) (Fan et al., 2007). The first step in this method is feature selection wherein regions that show high correlation between RAVENS maps and participant groups are extracted using a watershed algorithm. A further volume-increment algorithm is then applied to these regions to extract regional volumetric features, from which a feature selection method based on SVM classification criteria is used to identify the most relevant features for classification (Fan et al., 2007). The feature selection procedure produces a small number of volumetric measurements for

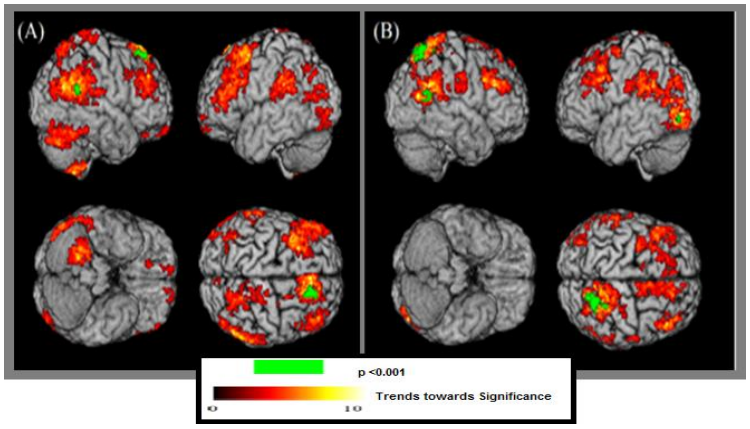
more effective classification. The SVM classification technique with the most distinguishing features is then used to predict group differences using the leave one out cross validation strategy (Fan et al., 2007).

5.3 Results

5.3.1 Structural neuroanatomy (ODVBA analysis)

In grey matter density, reductions were revealed in the right superior frontal and superior temporal regions in MDD patients relative to healthy controls ($p < 0.001$, uncorrected) (Table 5.4, Figure 5.1). In white matter density, reductions were also evident in the right postcentral, superior parietal, middle temporal and left inferior occipital regions in MDD patients relative to healthy controls ($p < 0.001$, uncorrected) (Table 5.4, Figure 5.1).

Figure 5.1: Grey and white matter regions showing atrophy in MDD relative to controls



Grey matter regions showing atrophy in MDD patients relative to healthy controls. (b) White matter regions showing atrophy in MDD patients relative to healthy controls. Green indicates significant regions at $p < 0.001$, uncorrected. The area of hot colour (threshold $p < 0.05$) indicates the trend towards significance characterised by –log(p) values shown in the colour bar.

Table 5.4: Regions showing atrophy in MDD patients relative to healthy controls

Anatomical Region	Mass size	Talairach Coordinates		
		x	y	z
Grey Matter				
Right superior frontal	74	17.82	31.54	48.16
Right superior medial frontal	14	11.88	31.73	51.83
Right superior temporal	13	53.46	-43.64	20.60
White Matter				
Right superior parietal	212	21.78	-57.30	58.13
Right middle temporal	46	49.50	-51.57	17.31
Right postcentral	14	25.74	-41.80	57.36
Left inferior occipital	10	-37.62	-75.81	-1.25

There were no regions which showed greater volume in MDD patients relative to controls

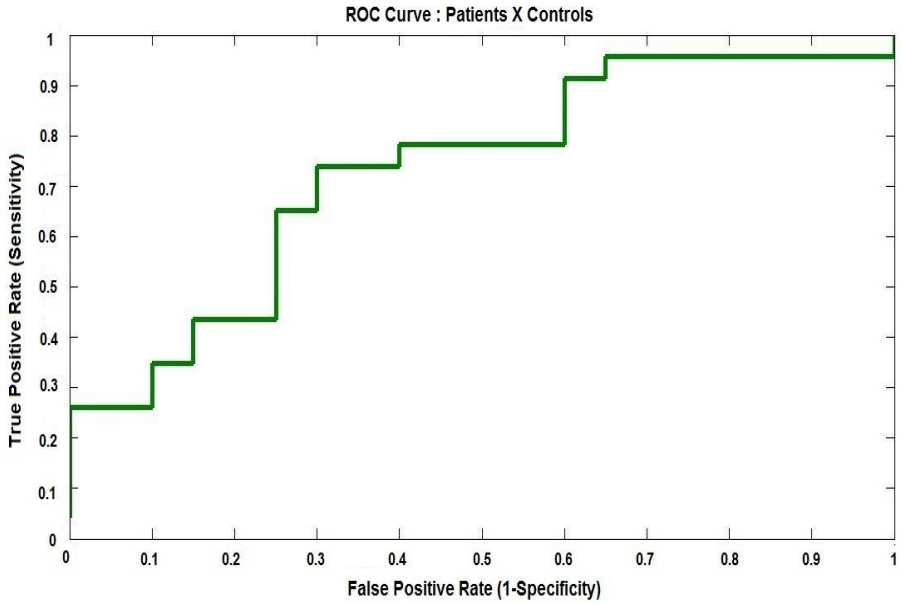
5.3.2 Diagnostic and prognostic classification using SVM

For diagnosis, the combination of grey and white matter density was able to correctly identify 78.3 % of MDD patients (sensitivity: 18 of 23 patients) and 55.0 % of healthy controls (specificity: 11 of 20 healthy controls) for an overall accuracy of 67.4 % (AUC = 0.73, p = 0.02) (Figure 5.2). Based on grey matter only, the accuracy of diagnosis was 60**.**47 %, but this did not reach statistical significance (AUC = 0.55, p = 0.2), while with white matter density alone, the accuracy was 65.1 % (AUC = 0.73, p = 0.05). Several white matter regions in the superior and medial frontal gyri, superior parietal, inferior occipital gyri and the cerebellum contributed towards the identification of MDD patients (Figure 5.3).

In predicting clinical remission, the accuracy was 51.40 % from combined grey and white matter densities (AUC = 0.42), which did not reach statistical significance. Similarly, the accuracy for grey matter (57.0 %; AUC = 0.40) and white matter (57.3 %, AUC = 0.44) did not reach statistical

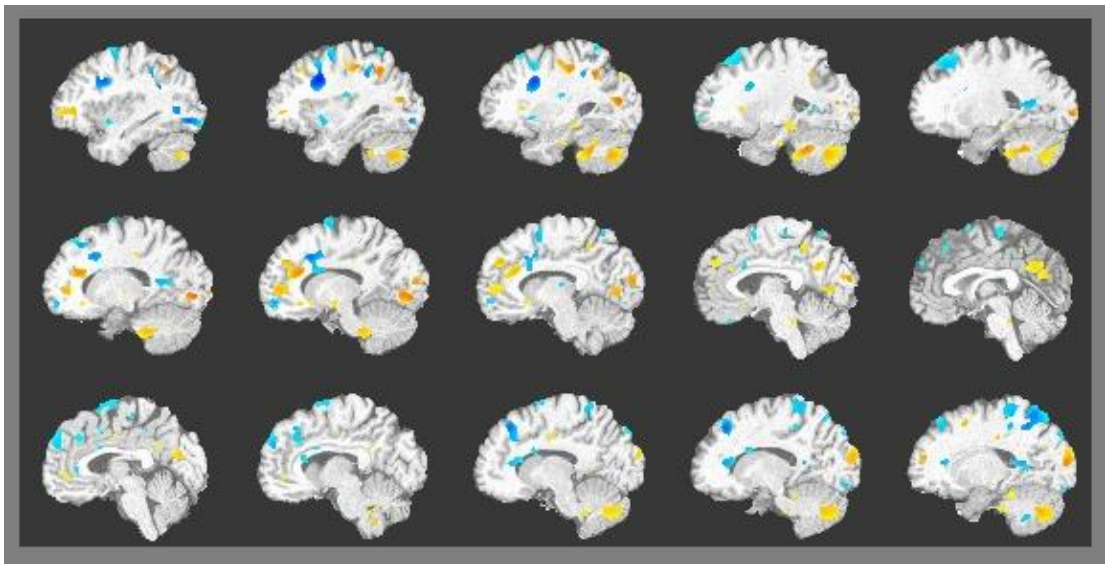
significance. Structural biomarkers of clinical response were not examined as the majority (82.6%) of patients fulfilled criteria for clinical response following treatment.

Figure 5.2: ROC Curve for the comparison between MDD patients and healthy volunteers



Area under Curve (AUC) = 0.73

Figure 5.3: p map for diagnostic classification

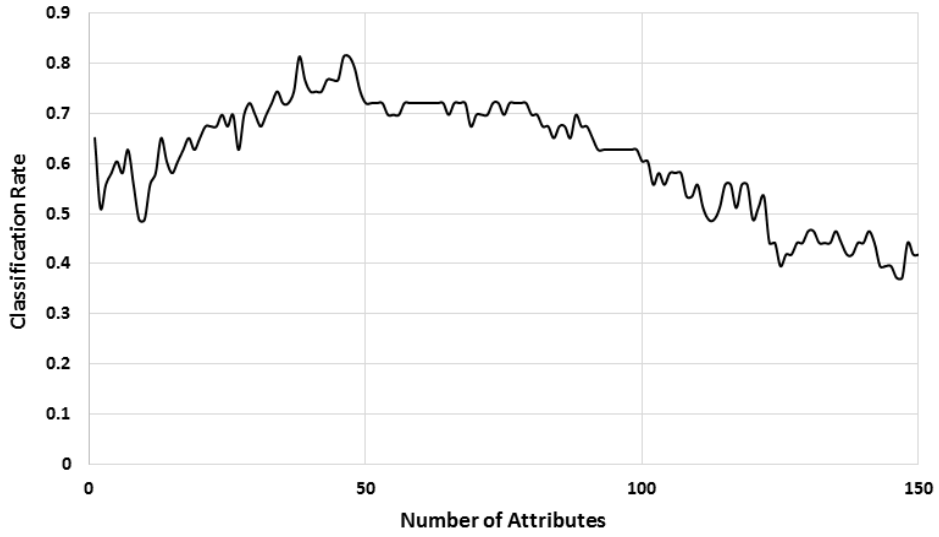


p map showing white matter regions that contributed towards diagnostic classification of depression at $p < 0.05$, uncorrected. Blue indicates regions showing atrophy in MDD patients relative to controls, while yellow indicates greater volume in MDD patients compared with healthy control subjects.

5.3.3 Diagnostic classification from COMPARE analysis

With the inclusion of feature selection in the COMPARE analysis (Fan et al., 2007), the best classification rate obtained was 81 % with 47 features. A relatively stable pattern with an accuracy of around 70 % was achieved with 50 - 70 features (Figure 5.4).

Figure 5.4: Graph illustrating change in classification rate with number of attributes



5.4 Discussion

In the present study, potential of structural data to predict diagnosis of depression as well as predict clinical remission to duloxetine, an antidepressant of the SNRI class, were examined. The results revealed that white matter was better at predicting diagnosis (accuracy 65.12 %: AUC = 0.73, p = 0.05), and yielded statistically significant results compared to grey matter (accuracy of 60.46 %, AUC = 0.55, p = 0.2). However, combined evaluation of grey and white matter did not significantly improve classification rates (accuracy 67.44 %, p = 0.02). In contrast, the present study revealed that the whole brain structural correlates of depression showed limited potential as a prognostic marker.

It was notable that the highest accuracy was achieved from combining grey and white matter features in the structural MRI scans. A widespread network of the superior and medial frontal gyri, superior parietal and inferior occipital regions was found to contribute towards diagnostic classification. The present findings are in line with recent studies that confirm the potential of combined grey and white matter in diagnostic classification (Gong et al., 2011; Liu et al., 2012). Univariate VBM studies have consistently reported grey matter deficits in MDD in the frontal regions, including the dorsolateral prefrontal cortex, inferior and medial frontal gyrus (see meta-analyses: Bora et al., 2012; Atkinson et al., 2014). Other regions include the anterior cingulate, insula, (Bora et al., 2012; Atkinson et al., 2014), putamen, precentral gyrus (Bora et al., 2012), post central gyrus, parahippocampal gyrus and the thalamus (Atkinson et al., 2014). More recently, investigations of white matter abnormalities in MDD patients have also reported volume reductions as well as reduced fractional anisotropy (FA), a measure of brain connectivity derived from DTI studies, in the frontal (Volume: Steingard et al., 2002; FA: Ma et al., 2007; Wu et al., 2011; also see meta-analysis: Liao et al., 2012), parietal (Volume: Zeng et al., 2012; FA: Ma et al., 2007; Wu et al., 2011) and occipito- temporal (FA: Ma et al., 2007) white matter regions. Moreover, greater deficits in white matter integrity was also associated with more severe symptoms (Cole et al., 2012). These findings suggest widespread white matter abnormalities in MDD patients in addition to grey matter atrophy, which may worsen with depression severity.

Both Gong et al. (2011) and Liu & colleagues (2012) showed that white matter could distinguish treatment sensitive patients (85 % and 91 % respectively), better than treatment resistant ones (59 % and 86 % respectively) from healthy controls. Consistent with the results obtained here, white matter regions in the frontal, parietal, and occipital lobes differentiated treatment sensitive patients from controls (Gong et al., 2011; Liu et al., 2012). These included the middle frontal, inferior parietal, supramarginal and lingual gyri (Gong et al., 2011; Liu et al., 2012) as well as the anterior and posterior cingulate, precuneus and inferior occipital regions (Liu et al., 2012). Further research is required to confirm the finding of improved diagnostic accuracy with treatment sensitive patients

as one would expect greater structural differences between treatment resistant patients and controls, than between treatment sensitive ones and controls.

The results also revealed that white matter regions in the bilateral cerebellum contributed towards diagnostic classification. There is increasing evidence to suggest that the role of the cerebellum may not be limited to motor control and coordination, but may also involve other cognitive functions including emotional processing and regulation of emotional responses (Schmahmann & Caplan, 2006; Baumann & Matingley, 2012). Neuroanatomical studies have rendered further support for the involvement of cerebellum in emotional processing with different regions of the cerebellum, especially the vermis and the fastigial nucleus, showing connections with the limbic system including the amygdala, hippocampus and the cingulate cortices (Blatt et al., 2013). Findings from multivariate pattern analysis studies suggest that grey matter regions in the cerebellum differentiated patients from controls (Costafreda et al., 2009b; Liu et al., 2012), while the predictive power of cerebellar white matter was limited to differentiating treatment resistant patients from controls (Liu et al., 2012). Additionally, resting state cerebellar-cerebral connectivity (Ma et al., 2013), especially connections between the cerebellum and regions of the affective and default mode networks (Zeng et al., 2014) also showed high discriminative power for diagnosis. It is important to note that some pattern recognition studies in depression have excluded the cerebellum for investigation (ex. Kipli et al., 2013; Qiu et al., 2014; Serpa et al., 2014), which may have contributed to this region being underreported, and therefore requires further examination.

In addition to pattern classification using SVM, analysis of regional group differences in grey and white matter between MDD patients and controls was also performed. Results from the ODVBA analysis showed grey matter atrophy in the right superior frontal gyrus in acutely depressed MDD patients relative to controls. Studies based on VBM analysis have also showed decreased grey matter volume in this region in patients with sub-threshold depression (Taki et al., 2005), in patients in an acute episode (meta-analysis: Atkinson et al., 2014), and in remission (Li et al., 2010), relative to healthy control subjects. The superior frontal gyrus is thought to be involved in a variety of

cognitive functions, especially in working memory (du Boisgueheneuc et al., 2006). Grey matter loss in the superior frontal gyrus in MDD patients in an acute episode is consistent with results that show working memory deficits in this group (Rose & Ebmeier, 2006). In addition, results also showed reduced grey matter volume in the superior temporal region ($p < 0.001$, uncorrected), in line with studies that showed grey matter loss in this region in both acutely depressed MDD patients (Takahashi et al., 2010) and in chronically depressed treatment-resistant group (Shah et al., 1998). Moreover, specific sub regions of the superior temporal gyrus, such as the temporal pole were negatively associated with depression scores (Takahashi et al., 2010).

In addition to grey matter loss, MDD patients also showed significant reductions in white matter volume in the right postcentral gyrus, superior parietal, middle temporal and left inferior occipital regions ($p < 0.001$, uncorrected). Majority of the studies in major depression examining white matter have used DTI to investigate microstructural changes (ex. Alexopoulos et al., 2002; Taylor et al., 2004; Bae et al., 2006; Nobuhara et al., 2006; Ma et al., 2007; Wu et al., 2011) and a considerable number of these studies have focussed on geriatric depression (ex. Alexopoulos et al., 2002; Taylor et al., 2004; Bae et al., 2006; Nobuhara et al., 2006). Fewer studies have examined volumetric abnormalities in white matter in major depression and evidence has shown increases in the dorsolateral prefrontal cortex and putamen (Zeng et al., 2012), deceases in the frontal (Steingard et al., 2002), cerebellar and inferior parietal regions (Zeng et al., 2012), as well as no volumetric differences in white matter (Kim et al., 2008; Abe et al., 2010) in MDD patients relative to healthy controls. Further investigations of white matter volume in different depressive states (ex. acute episode, in recovery or in remission) and alterations with treatment are required.

Interestingly, temporal regions have also shown the potential to discriminate treatment sensitive (Liu et al., 2012) and treatment resistant (Gong et al., 2011; Liu et al., 2012) patients from control subjects using multivariate pattern recognition, though this finding could not be replicated in the SVM analysis. While the SVM analysis in this study was unable to detect findings in the temporal regions for diagnostic prediction, the voxel-based analysis between patients and controls using

ODVBA showed significant reductions in grey and white matter in temporal regions in patients relative to controls. It is likely that the small sample size may have led to insufficient power to detect all findings that contributed towards diagnosis prediction.

A limitation of the present study is the relatively small sample size, although comparable to previous studies (Gong et al., 2011; Liu et al., 2012; Mwangi et al., 2012). Advantages of the current sample include their medication-free status while in an acute depressive episode as all patients had not been taking any medications for a minimum of 4 weeks, while one of the highest classification accuracy was observed in patients who were already on antidepressant medications (Mwangi et al., 2012); inclusion of patients in their first episode as well as having recurrent episodes; and their wide ethnicity which included Asian, African and Caucasian participants.

In summary, the whole brain structural correlates showed limited potential for prognosis. Nevertheless, the present study showed that structural neuroanatomy combining white and grey matter distinguished patients from controls at the highest accuracy of 81% with the most stable pattern being at around 70%. A widespread network encompassing frontal, parietal, occipital and cerebellar regions contributed towards diagnostic classification. These findings provide an important step in the development of potential neuroimaging-based tools for diagnosis.

6 General discussion

This chapter opens with a review of the aims and objectives of this work. Next, a brief treatment of the contextual situation of this research in relation to previous work is attempted. Then, the chapter provides a summary of the key findings from the individual studies presented; these findings are also compared with and discussed in view of other existing work. Lastly, limitations of the present work and avenues for extension and future research are suggested.

The preceding chapters of this work are organised around cores that each focus on one or two self-contained questions. However, there are shared themes and goals that overarch these cores as well as common threads that weave the individual studies together. These have not been discussed so far, as the earlier chapters dwelt on somewhat distinct research questions. Thus, in this chapter, I attempt to cover this essential yet uncharted territory.

6.1 Aims and objectives

The main objective of this thesis is to examine the neural correlates of affective and cognitive processing in depression and how they change with treatment. This is of interest due to the significant need for improving treatment strategies available for depression. Using magnetic resonance imaging, it has been possible to examine the neuropsychological mechanisms of antidepressant drug action and psychotherapies that lead to clinical response. This has particular implications in the development of novel treatment strategies or in the augmentation of existing therapeutic interventions. So, this work seeks to investigate the dysfunctional brain activations in depression, and how it might normalise with treatment by leveraging fMRI technology.

In order for neuroimaging findings to have tangible clinical applications, it is important that we are able to develop biomarkers that can predict therapeutic response in MDD with high accuracy at the individual level. Therefore, another key focus in the thesis is to examine the potential of structural neuroimaging data to identify depression and predict clinical remission using machine learning

algorithms. This is significant as it helps optimize treatment strategies at an early stage. In particular, this means we can provide alternate treatment options early on for those who are less likely to benefit from conventional methods.

6.2 Survey of extant work and motivation

In the first chapter, longitudinal studies that examined the effects of antidepressant treatment and psychological therapies on the neural correlates of affective and cognitive processing are reviewed. These neuropsychological aspects are especially chosen since there is a sizeable body of research associating them with depression.

With functional MRI, it has been possible to examine patterns of regional brain activations associated with affective and cognitive impairments in depression that contribute to the maintenance of the disorder and how they normalise with successful treatment. Findings from previous studies suggest that antidepressants regulate dysfunctional activity in limbic regions, in particular the amygdala, as well as in subcortical and prefrontal regions in patients during processing of emotional and cognitive stimuli (Sankar & Fu, in press). However, majority of these studies focussed on the SSRI class of antidepressants (meta-analysis: Delaveau et al., 2011). Owing to the scarcity in longitudinal studies examining treatment strategies other than SSRIs, it is unclear whether the regional changes seen after treatment is specific to a class of pharmacotherapy; or whether such changes are common across different classes of antidepressant drugs and even across different treatment modalities.

Three chapters in this work attempt to bridge this gap in the literature. Chapter 2 investigated the effects of CBT on dysfunctional thinking in major depression. The effects of a dual acting SNRI, duloxetine, on affective and cognitive impairments in depression were examined here in two separate branches of their own (Chapters 3 and 4).

Besides examining the differential neural effects of pharmacological and psychological therapies in depression, identifying clinically useful biomarkers of diagnosis and treatment response is also crucial. Previous studies that examined the potential of neuroimaging measures, especially structural imaging data to identify biomarkers in depression have several limitations: homogenous ethnic group (Chinese: Gong et al., 2011; Liu et al., 2012; Qiu et al., 2014; Caucasian: Costafreda et al., 2009b; Mwangi et al., 2012), restriction to treatment-naïve MDD patients (Liu et al., 2012; Qiu et al., 2014), inclusion of medicated MDD patients (Mwangi et al., 2012), heterogeneous antidepressant treatment (Gong et al., 2011; Liu et al., 2012) and inclusion of grey matter only (Costafreda et al., 2009b). These limitations have been addressed in Chapter 5 in the SVM analysis which included medication-free patients of white, Asian and African descent, incorporating both first episode MDD patients as well as those at a later stage of the disorder who were all initially medication-free during an acute depressive episode and who then received a stable dose of a single drug duloxetine belonging to the SNRI class, and investigating the potential of both grey and white matter in predicting diagnosis and prognosis.

6.3 Propositions and findings

In the following paragraphs, key findings from each Chapter are discussed in brief

6.3.1 ***Chapter 2:*** *Longitudinal fMRI study: neural effects of cognitive behavioural therapy on dysfunctional thinking in depression.*

6.3.1.1 ***Behavioural findings***

The present study supports a modifying effect of CBT on dysfunctional attitudes (Haaga et al., 1991; Furlong & Oei, 2002) as patients endorsed a greater number of extreme responses to DAS statements during an acute depressive episode which normalised following CBT.

6.3.1.2 Neuroimaging findings

Neural correlates revealed greater activations in depressed patients relative to controls in the left hippocampal gyrus, left inferior parietal lobule and the left precuneus, which are regions associated with attentional processing of emotional stimuli and episodic memory retrieval. This suggests that when the DAS statements are presented, depressed patients, compared to controls, engage more in attentional processing of the statements, along with active retrieval of memories associated with them. The hippocampus, precuneus (Fu et al., 2004; Ritchey et al., 2011) and inferior parietal gyrus (Fu et al., 2004; Fu et al., 2008; Wang et al., 2012) have also showed increased activity in patients relative to controls in response to sad facial processing (Fu et al., 2004) and negative pictures (Ritchey et al., 2011; Wang et al., 2012), perhaps reflecting a more general response to negative emotional stimuli, rather than a specific response to negative styles of thinking. The group by time interactions for extreme attributions showed significant reductions in the parahippocampal gyrus in both groups at follow up scan, though to a lesser extent in MDD patients. To date, there has been no fMRI study that has investigated the neural correlates of dysfunctional attitudes in depression, and therefore one cannot make direct comparisons to confirm the role of parahippocampal gyrus in dysfunctional attitudes. However, the left parahippocampal activation seems to be especially associated with negative stimuli (Iidaka et al., 2002; Surguladze et al., 2005), and activation in this region in both patients and in controls during presentation of DAS statements supports the role of the left parahippocampal gyrus in processing negative information contained in the DAS statements. The reduction in parahippocampal activation with time is consistent with increased familiarity with repetition of the task, although patients did not demonstrate the same extent in the reduction in activation. This may perhaps reflect patients' inability to recall the task in the same manner as controls, likely due to persistent engagement and contextual associations to the DAS statements.

6.3.2 ***Chapter 3:*** *Longitudinal fMRI study: effects of a dual serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine on the processing of sad and happy facial expressions.*

6.3.2.1 ***Behavioural findings***

Behavioural responses showed limited difference between the groups, especially for sad facial processing. Although, evidence from previous studies suggest that MDD patients show biases in negative facial processing (Fu et al., 2004; Surguladze et al., 2005; Arnone et al., 2012), studies have also observed patients to perform as well as controls in tasks of negative facial processing (ex. Lee et al., 2008; Frodl et al., 2011) consistent with findings from the present study.

6.3.2.2 ***Neuroimaging findings***

Longitudinal neuroimaging studies have showed normalisation of cortico-limbic activity, especially in the amygdala (Fu et al., 2004; Arnone et al., 2012), insula (Fu et al., 2004) and anterior cingulate (Fu et al., 2004; Victor et al., 2013) following treatment with antidepressants. Contrary to these findings, the present study did not reveal any main effects of group or group by time interactions for sad facial expressions. However, there was a main effect of time with increases in the posterior cingulate gyrus in MDD patients following 12 weeks of treatment with duloxetine. This is in line with findings that show increases in this region with antidepressants that potentiate the noradrenergic systems (Kennedy et al., 2007; Brühl et al., 2010; Outhred et al., 2013). In contrast, treatment with SSRIs is especially associated with decreases in the posterior cingulate gyrus (see meta-analysis: Delaveau et al., 2011).

Happy facial expressions on the other hand have shown some evidence of decreased activation in MDD patients relative to healthy controls in the amygdala (Lawrence et al., 2004). However, a considerable number of studies that examined neural correlates of positive emotional stimuli have also failed to observe significant group differences (Fu et al., 2007; Arnone et al., 2012; Rosenblau et al., 2012) or any group by time interaction effects (Davidson et al., 2003; Fu et al., 2007) in the

amygdala. In the present study, there were no significant main effects of group or any group by time interaction effects in response to happy facial expressions. The results from the happy and sad facial processing study may reflect some distinct effects of the SNRI class of antidepressants during sad facial processing; however, further placebo controlled investigation with a larger sample is required to confirm present findings.

6.3.3 Chapter 4: Longitudinal fMRI study: effects of a dual serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine on working memory

6.3.3.1 Behavioural findings

The behavioural responses in the present study did not reveal any significant difference between the groups in working memory, consistent with findings from previous studies using different working memory paradigms (ex. n-back: Harvey et al., 2005; Rose et al., 2006; Matsuo et al., 2007, Sternberg: Siegle et al., 2002). Memory impairments in depression may be more likely in severely depressed patients who need hospitalization (ex. Sternberg et al., 1976). The sample used in this study comprises patients with a less severe form of depression, and are representative of patients found in the community. Another factor that influences cognitive impairment is the difficulty level of these tasks (Porter et al., 2003). It is likely for MDD patients in this study to show impairments in working memory if they are assigned a more cognitively challenging task.

6.3.3.2 Neuroimaging findings

In this study, there were no significant differences between the groups during the encoding, rehearsal or retrieval stages. However, during encoding, MDD patients showed a trend for reduction in regions associated with working memory, such as the prefrontal regions, middle and inferior temporal, cingulate and the inferior parietal gyri. The results from this study are consistent with previous PET findings that showed reductions in MDD patients after treatment in the middle/superior frontal, inferior temporal gyrus, and parietal regions during encoding (Bremner et

al., 2007). Findings from the present study only show a trend for significance in these regions, however variations in the imaging technique employed, and the use of what may be perceived as a more liberal threshold ($p < 0.005$ with extent threshold of 40 voxels) in Bremner et al. (2007) may have contributed to some of the differences in effect size. Treatment related decreases during retrieval in this study were also seen in a similar network of regions encompassing the prefrontal, temporal and mid cingulate gyri (cluster level $p_{FWE} < 0.05$); and decreased baseline activations in these regions during verbal working memory were associated with better clinical response (Walsh et al., 2007).

The neural correlates also showed a significant group by time interaction during the long rehearsal phase such that there was a tendency for reductions in brain activations post treatment (week 12) relative to baseline (week 0) in controls in regions extending from the middle frontal, caudate/thalamus, mid cingulate, to the temporal and cerebellar areas, while no change was observed in patients. There was also a group by time interaction in the superior temporal gyrus and this effect was due to patients showing a tendency for decreased activation in the final scan. The neural correlates of n-back working memory in healthy controls constitute a network of region comprising the dorsal cingulate, medial and inferior frontal regions, premotor cortex, frontal poles and posterior parietal regions (Owen et al., 2005). The present study found significant group by time interaction within this network. Walsh et al. (2007) also found a group by time interaction in the caudate and thalamus with fluoxetine in response to a verbal working memory task, whereby controls showed a decrease in activation with time, while the opposite effect was seen in patients. In the present study, tendency for decreased activations in controls in the follow up scan is perhaps indicative of less recruitment of these regions with increased familiarity with the task, while no change in activation in patients may reflect persistent recruitment of regions associated with working memory to maintain task performance.

Longitudinal imaging studies in working memory in depression are limited (ex. Bremner et al., 2007; Walsh et al., 2007) and they have either not examined the effects of treatment on maintenance

related activations (ex. Bremner et al., 2007) or used the n-back task that did not differentiate activations associated with the different working memory processes (ex. Walsh et al., 2007). The findings from the present study must be considered preliminary and further placebo-controlled investigations with larger sample are required to confirm present findings and delineate antidepressant effects from changes associated with clinical improvements.

*6.3.4 **Chapter 5:** Machine learning study: diagnostic and prognostic potential of structural neuroimaging data in depression using Support Vector Machines (SVM).*

*6.3.4.1 **Neuroimaging findings***

Structural neuroanatomy distinguished acutely depressed patients from healthy controls with an accuracy of 67.44 % using SVM (Sensitivity = 78.3%; Specificity = 55 %, p = 0.02). With the inclusion of feature selection, the best classification rate obtained was 81 % with 47 features. A relatively stable pattern with an accuracy of around 70 % was achieved with 50 - 70 features. In previous studies that used structural MRI scans (see Table 5.1), the accuracy of diagnosis for depression has ranged from 58 % to 90 % (see Costafreda et al., 2009b; Gong et al., 2011; Liu et al., 2012; Mwangi et al., 2012; Kipli et al., 2013; Qiu et al., 2014; Serpa et al., 2014). In the present study, a widespread network of white matter encompassing frontal, parietal, occipital regions and cerebellum contributed towards diagnostic classification. A meta-analysis examining neuroimaging biomarkers of schizophrenia revealed that patients could be differentiated from controls using structural MRI data with a sensitivity of 76.4 % and specificity of 79 % (Kambeitz et al., 2015). In the present study, an accuracy of 81 % was achieved, although the most stable findings were at an accuracy of around 70 %. One would expect a higher accuracy for the diagnosis of schizophrenia, which is associated with greater global brain volume reductions, extensive regional atrophy as well as white matter disruptions (Bora et al., 2011).

In contrast with findings from the diagnostic predictions, whole brain structural correlates of depression showed limited potential as a prognostic marker. In summary, the findings from this

study provide an important step in the development of neuroimaging-based tools for diagnosis as they demonstrate that the identification of depression is feasible within a multi-ethnic group from the community.

6.4 Summary of key findings

In summary, the studies presented in the thesis examined the neural effects of treatment on different features of depression, namely affective biases, dysfunctional thinking and working memory impairments. To mitigate concerns regarding effects of comorbid diagnoses or concomitant treatment on brain activity, that are often seen as limitations in other longitudinal neuroimaging studies, only those patients who were free of any psychotropic medication and psychological therapies for a minimum of four weeks, who were in an acute depressive episode, and who did not meet criteria for any comorbid psychiatric illness, or any medical disorders known to affect central nervous system structures or function such as diabetes, high blood pressure, HIV and glaucoma were included. Hence, findings from baseline analyses performed in these studies are likely to accurately reflect brain changes associated with an acute depressive episode. Due to ethical considerations, it was not possible to have a patient group arm receiving placebo, therefore it is difficult to conclude with certainty that the modulations in brain activations in patients during the follow up scan is as a result of treatment alone, rather than reflecting clinical improvements. Nevertheless, unlike many previous neuroimaging studies (ex. Robertson et al., 2007; Frodl et al., 2011; Jiang et al., 2012; Wang et al., 2012), main effects of time and effects of repeated scans were accounted for by having controls also undergo scans at the same time points as patients. Moreover, the statistical thresholds used in the duloxetine study to examine group differences and treatment related effects are in accordance with the most recent recommendations (Woo et al., 2014) to effectively minimise type I and type II errors.

In the present study, functional neuroimaging correlates showed antidepressant treatment related increases in the posterior cingulate in MDD patients during sad facial affect processing, in line with preliminary findings that show increases in this region with antidepressants that potentiate the noradrenergic systems. No baseline group differences in either happy or sad facial affect processing was observed, suggesting poor test-retest reliability of such fMRI paradigms to detect limbic activity (Fu et al., 2015; Sauder et al., 2015). The neural correlates of working memory, on the other hand, showed a significant group by time interaction during the long rehearsal phase, such that there was a tendency for reductions in brain activations at the follow up scan compared to baseline in controls in a network of brain areas extending from the prefrontal, to the cingulate, temporal and cerebellar regions, while no change was observed in patients. This decreased activations in controls in the follow up scan is perhaps indicative of less recruitment of these regions with increased familiarity with the task, while no change in activation in patients may reflect persistent recruitment of regions associated with working memory to maintain task performance. Findings from the study that examined the neural effects of CBT on dysfunctional attitudes showed less attenuation in patients relative to controls during follow up, perhaps reflecting improvements in dysfunctional thinking in patients with some persistent vulnerability. Further placebo-controlled investigations with larger sample are required to confirm findings from the individual studies and delineate antidepressant effects from changes associated with clinical improvements.

Another focus of the thesis was to examine whether structural neuroanatomy could identify depression and predict clinical remission using machine learning techniques. The structural neuroanatomy showed limited potential for predicting clinical outcome. Nevertheless, the present study showed that structural neuroanatomy combining white and grey matter distinguished patients from controls at the highest accuracy of 81% with the most stable pattern being at around 70%. The study demonstrates that identification of depression is feasible using structural neuroimaging data in

a sample of wide ethnic diversity taken from the community, and provides an important step in the development of potential neuroimaging-based tools for diagnosis

6.5 Limitations

6.5.1 Participants

The study included medication-free patients who were, at the time of recruitment, in an acute episode of depression of at least moderate severity. The sample exhibited features of depression most commonly observed in the community. However, patients with any comorbid psychiatric illness were excluded, and the sample may not completely represent the general MDD profile as major depression is often associated with other comorbid illnesses such as anxiety disorders.

Majority of the patients in the CBT as well as the duloxetine studies responded to treatment. This in part reflected the increased likelihood of patients recruited from the community to engage with services. None of the patients were recruited from secondary care who may be less responsive to treatment. The high response rate in the studies presented in the thesis limited the power to detect neural differences between responders and those with a more chronic form of the disorder, which may be associated with distinct neural correlates (Fu et al., 2008a). Another limitation is that the small sample size, although comparable to other studies (ex. Fu et al., 2004, 2007,2008; Fales et al., 2009; Frodl et al., 2011; Ruhe et al., 2012), may have led to insufficient power to detect all neural differences.

6.5.2 Methodological considerations

There was no treatment group receiving placebo. So, the attribution of changes to treatment (whether CBT or antidepressant) as opposed to temporal clinical improvement is not obvious.

However, potential effects of time were accounted for by having healthy participants undergo scans at the same time points as MDD patients.

Although, in this thesis, the effects of both cognitive behavioural therapy as well as pharmacological treatment on the neural correlates of emotional processing in depression were examined, different functional tasks were used in the examination of these. Comparison on a single task is desirable for a more accurate account of the common and distinct therapeutic mechanisms of action of both treatment modalities. However, an advantage of the works presented in this thesis is that they extensively examine the neural effects of treatment on different features of depression (ex. affective biases, cognitive impairments and dysfunctional thinking) and therefore the different paradigms and findings from the individual studies complement each other.

6.5.3 Task design

In **Chapter** 2, the DAS 24 (Power et al., 1994) was used, which is a shortened version of the DAS (Weissman & Beck, 1978) consisting of twenty four statements. Twenty four neutral statements were included as a control task for the present study, which were called control DAS (cDAS). The new forty eight item scale was termed the 'modified Dysfunctional Attitude Scale' (mDAS-48). Additional investigation comparing neural responses during extreme attributions to positive statements with that of responses during negative statements would help understand the nature of dysfunctional thinking in relation to different valenced stimuli.

In **Chapter** 3, the neuroimaging findings failed to show any significant pre-treatment differences between MDD patients and controls in amygdala activations in response to either happy or sad facial expressions, contrary to the study hypothesis. This in part may be due to poor test-retest reliability of amygdala response to emotional facial paradigms (Sauder et al., 2013; Fu et al., 2015).

In **Chapter** 4, an event related fMRI task, the Sternberg Item Recognition Task was used to examine working memory deficits in MDD patients. Although such designs permit dissemination of encoding, maintenance and probe related activations, the task is designed in a way that the

different working memory processes immediately follow one another in time. As an event, each of these working memory processes is discrete, however the associated BOLD response to each event may overlap with the successive event (Manoach et al., 2003). To counter this problem, Manoach et al. (2003) used an event related approach whereby trials with only encoding and probe phases were subtracted from trials that incorporated all three working memory processes (i.e. encoding, delay and probe phases). This method, along with Finite Impulse Response (FIR) models to estimate haemodynamic responses for the working memory trial, allowed separation of maintenance related activations from encoding and probe or retrieval associated activations (Narayanan et al., 2005).

6.6 Future directions

Although the findings from this work cannot be taken as conclusive, it nevertheless provides compelling evidence for the neural effects of treatment on different features of depression (ex. affective biases, working memory impairments and dysfunctional thinking) and demonstrates that the identification of depression is possible within a multi-ethnic group from the community. Yet, further studies are required to address some of the limitations found here. In the present work, patients with comorbid illnesses were excluded, and the relatively small sample size and high response rate limited the comparison of neural responses in treatment non-responders in contrast to responders. Future studies with a much larger sample size may benefit from including MDD patients with varied symptomatic profile and with comorbid illnesses such as anxiety as they often occur alongside major depression.

Longitudinal studies in major depression provide initial evidence for neural targets of successful treatment. It has been proposed that treatment with psychotherapy significantly impacts the brain regions involved in emotion processing disturbances in MDD patients. Not only have such studies been limited in number, but they have contained variations with respect to treatment, treatment

duration, and task processing. More work of greater homogeneity would appreciably supplement this area.

The machine learning findings provide preliminary evidence to suggest that the identification of depression is possible within a multi-ethnic group from the general community. Future research should aim to investigate whether integration of neuroimaging biomarkers based on multiple neural processes, such as affective and cognitive processing and structural neuroimaging, would achieve more accurate classification.

Majority of the studies in depression have looked at diagnostic prediction using SVM based classifiers. Other approaches, for instance, Random Tree classifier have also produced high predictive accuracy rates for diagnosis in depression using structural neuroanatomy (Kipli et al., 2013). There is a need for further research exploring possible classifiers that are better able to predict diagnosis and clinical response.

Another possible avenue for research is examining neural correlates of cognitive processing in patients that differ in depression severity, as cognitive impairments, especially episodic memory, is correlated with severity (meta-analysis: McDermott & Ebmeier, 2008). Moreover, the effect of CBT in cognitive functioning has not been previously examined and is of interest as one of the main aims of CBT is to alleviate attention and memory biases that lead to the maintenance of the disorder (Beck, 1979). These findings could throw light on the extent of neural impairments in relation to severity, factors contributing to non-response and avenues for treatment development.

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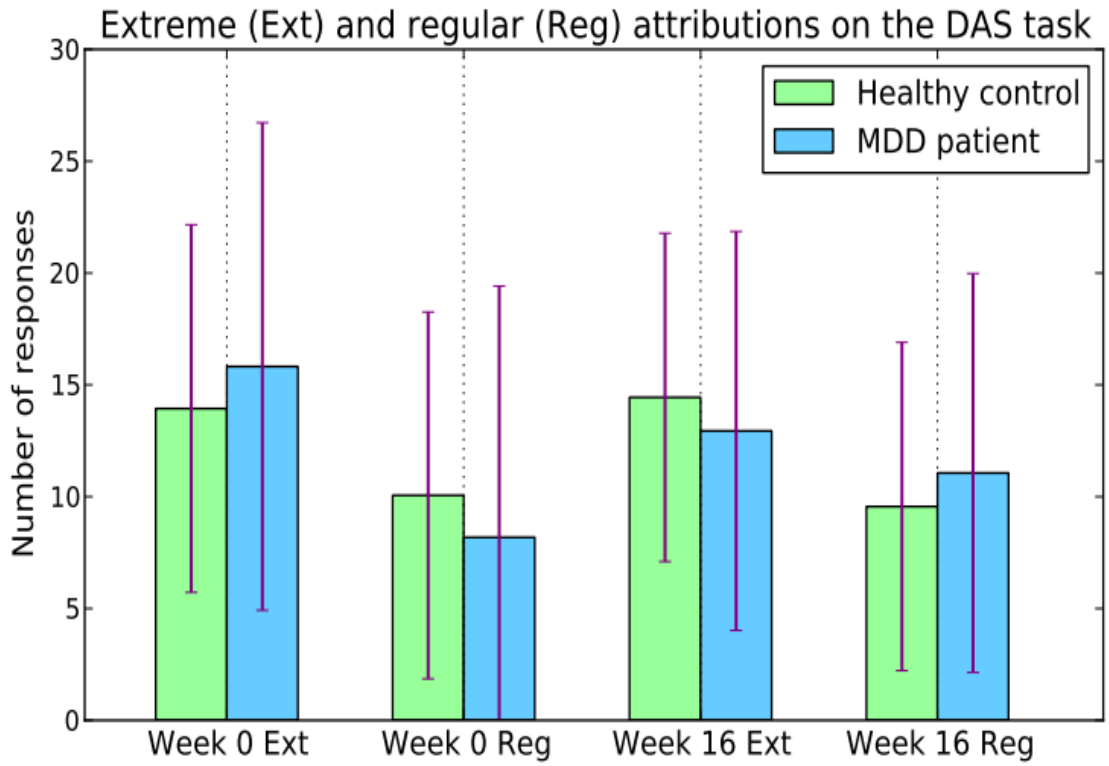
Supplementary section

Supplementary material 1

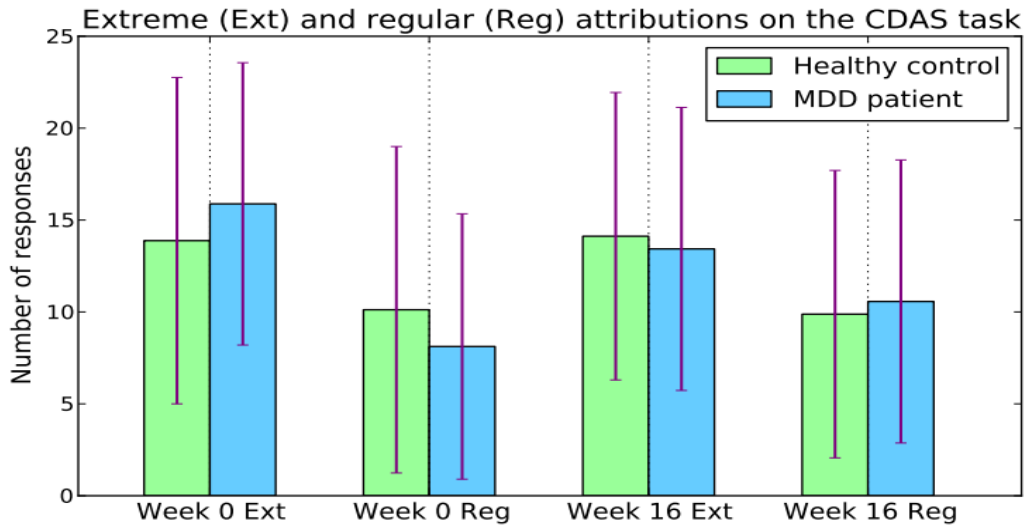
a. Behavioural results

Figure S1.1: Number of extreme and regular attributions on the DAS task for MDD patients and healthy controls



Ext: Extreme attributions; Reg: Regular attributions; DAS: Dysfunctional Attitude Statements

Figure S1.2: Number of extreme and regular attributions on the control DAS task for MDD patients and healthy controls



Ext: Extreme attributions; Reg: Regular attributions; cDAS: control statements

b. fMRI results

Main effect of group at baseline (week 0)

MDD patients showed increased activations in the left cuneus relative to healthy control subjects (corrected $p < 0.004$) during an acute depressive episode at the baseline scan (Supplementary Table S1.1). In contrast, controls showed greater activations than patients in the left cerebellum (corrected $p < 0.004$).

Main effect of group at baseline (week 0)

Following a course of CBT, the main effect of group revealed increased activations in patients in the left precuneus, left cerebellum and right lingual gyrus (all corrected $p < 0.003$) as compared with healthy controls. Healthy controls showed increased activation in the superior frontal gyrus and right cerebellum (all corrected $p < 0.003$) at the follow up scan as compared to patients (Supplementary Table S1.1).

Table S1.1: Main effect of group at baseline and at follow up

Cluster Region	Cluster Size (Volume)	BA	Talairach coordinates		
			x	y	z
Baseline (Week 0)					
Patients>Controls					
Left Cuneus	54	18	-7	-85	7
Controls>Patients					
Left Cerebellum	12	18	-7	-70	-16
Follow up (Week 16)					
Patients>Controls					
Right Lingual Gyrus	43	18	4	-74	-7
Left Precuneus	37	19	-22	-63	49
Left Precuneus	15	71	0	-59	53
Left Cerebellum	15	18	-18	-74	-13
Controls>Patients					
Right Cerebellum	52	30	14	-41	-20
Right Superior Frontal Gyrus	42	32	11	48	33

Main effect of task at baseline (week 0)

All subjects showed significant activation in the left middle frontal gyrus, left fusiform gyrus, left lingual gyrus, right cuneus and right cerebellum in response to the DAS statements as compared to the cDAS statements. Significant activations in the right cingulate gyrus and right superior frontal gyrus (all corrected $p < 0.006$) were observed in response to the cDAS statements as compared to the DAS statements (Supplementary Table S1.2).

Table S1.2: Main effect of task at baseline (week 0)

Cluster Region	Cluster Size (Volume)	BA	Talairach coordinates		
			x	y	z
DAS>cDAS					
Left Fusiform Gyrus	40	19	-33	-70	-13
Left Lingual Gyrus	54	18	0	-78	4
Left Middle Frontal Gyrus	57	72	-36	15	26
Right Cuneus	29	18	4	-78	17
Right Cerebellum	41	19	33	-63	-17
cDAS>DAS					
Right Cingulate Gyrus	104	22	18	59	17
Right Superior Frontal Gyrus	53	27	7	-37	33

Main effect of task following CBT (week 16)

All subjects showed significant activation in the left precuneus and bilateral cerebellum while viewing the DAS statements relative to the cDAS statements. Significant activations in the right middle temporal gyrus, right posterior cingulate gyrus and left cerebellum (all corrected $p < 0.006$) were observed in response to the cDAS statements as compared to the DAS statements (Supplementary Table S1.3).

Table S1.3: Main effect of task at follow up (week 16)

Cluster Region	Cluster Size (Volume)	BA	Talairach coordinates		
			x	y	z
DAS>cDAS					
Left Cerebellum	70	18	-18	-74	-13
Right Cerebellum	78	18	22	-70	-20
Left Precuneus	19	19	-25	-59	50
cDAS>DAS					
Right Posterior Cingulate Gyrus	392	71	3	-59	23
Left Cerebellum	130	70	-7	-33	-23
Left Cerebellum	62	71	-7	-48	3
Right Middle Temporal Gyrus	107	37	47	-59	17

Supplementary material 2

Table S2.1: **Sample response file generated for the facial expression paradigm**

Trial No	Gender	Response	Reaction Time	Accuracy	Start Time of Trial
1	Female	Female	827	Correct	0
2	Male	Male	673	Correct	4.148
3	Male	Male	681	Correct	7.524
4	Blank	.	.	.	12.497
5	Female	Female	901	Correct	18.35
6	Female	Female	603	Correct	22.628
7	Male	Female	677	Incorrect	27.033
8	Male	Male	595	Correct	30.524
9	Blank	.	.	.	34.191
10	Female	Female	1369	Correct	37.679
11	Female	Female	619	Correct	42.121
12	Male	Male	693	Correct	46.641
13	Female	Female	896	Correct	53.019
14	Blank	.	.	.	57.36
15	Male	Female	935	Incorrect	61.001
16	Female	Female	947	Correct	65.788
17	Male	Male	643	Correct	74.069
18	Female	Female	580	Correct	78.009
19	Male	Male	771	Correct	82.093
20	Female	Female	537	Correct	89.286
21	Blank	.	.	.	95.139
22	Female	Female	674	Correct	99.037
23	Male	Male	1164	Correct	106.432
24	Male	Male	913	Correct	110.331
25	Male	Female	1364	Incorrect	113.971
26	Female	Female	942	Correct	118.459
27	Female	Female	514	Correct	121.816
28	Female	Female	685	Correct	128.7
29	Male	Male	743	Correct	132.03
30	Blank	.	.	.	137.868
31	Male	Male	556	Correct	141.225
32	Male	Male	1035	Correct	147.861
33	Male	Male	724	Correct	152.165
34	Female	Female	503	Correct	160.809
35	Female	Female	533	Correct	164.66
36	Female	Female	567	Correct	169.824
37	Blank	.	.	.	173.972
38	Male	Male	599	Correct	181.367
39	Male	Male	555	Correct	185.743
40	Female	Female	871	Correct	190.716
41	Female	Female	513	Correct	194.994

Trial No	Gender	Response	Reaction Time	Accuracy	Start Time of Trial
42	Blank	.	.	.	199.399
43	Male	Female	853	Incorrect	207.68
44	Male	Male	544	Correct	211.171
48	Blank	.	.	.	229.178
49	Female	Female	535	Correct	232.965
50	Male	Female	601	Incorrect	237.306
51	Blank	.	.	.	241.093
52	Female	Female	583	Correct	245.177
53	Male	Male	675	Correct	253.458
54	Female	Female	684	Correct	257.398
55	Male	Male	669	Correct	261.482
56	Female	Female	697	Correct	268.675
57	Blank	.	.	.	274.529
58	Female	Female	529	Correct	281.721
59	Male	Male	604	Correct	289.116
60	Male	Male	1255	Correct	293.014
61	Blank	.	.	.	296.655
62	Male	Female	1102	Incorrect	300.595
63	Female	Female	1097	Correct	305.083
64	Female	Female	825	Correct	308.44
65	Female	Female	867	Correct	315.325
66	Blank	.	.	.	318.654
67	Male	Male	731	Correct	325.538
68	Male	Male	872	Correct	331.376
69	Male	Male	628	Correct	338.012
70	Male	Male	616	Correct	342.316
71	Female	Female	622	Correct	350.96
72	Female	Female	755	Correct	354.811

Supplementary material 3

Table S3.1: Sample response file generated for the modified Sternberg task

Trial	Cue	Target	Presence of Target	Response	Reaction Time	Accuracy	Cue Onset	Target Onset
1	N T X W V R	n	Yes	.	.	.	0	8
2	A Q B J H E	o	No	.	.	.	15	33
3	U D K M G Z	j	No	Yes	1245	No	40	48
4	I Y C S F L	l	Yes	Yes	1864	Yes	55	73
5	P R X O Q E	x	Yes	Yes	1354	Yes	80	98
6	T K A J N U	f	No	No	1161	Yes	105	113
7	V S H U Z B	s	Yes	Yes	1136	Yes	120	128
8	E Y L W F G	j	No	No	1204	Yes	135	153
9	X M I P R T	r	Yes	No	1228	No	160	178
10	J S C O Q A	e	No	.	.	.	185	193
11	K W N U H Z	u	Yes	Yes	1104	Yes	200	208
12	Y V F E G B	b	Yes	No	1706	No	215	233
13	M L D I R Q	i	Yes	Yes	1193	Yes	240	258
14	Z O J C X T	n	No	No	1507	Yes	265	273
15	B W H S V A	m	No	No	1079	Yes	280	298
16	N L K E I F	g	No	No	1400	Yes	305	313
17	D U P R S Q	w	No	No	1633	Yes	320	338
18	M G Y T X O	y	Yes	Yes	1093	Yes	345	363
19	F V C N I H	d	No	No	1415	Yes	370	378
20	W Z K A Q B	q	Yes	Yes	1270	Yes	385	393
21	G L E J S P	r	No	No	1275	Yes	400	408
22	O D T Y M U	i	No	Yes	1240	No	415	433
23	C R F H X A	c	Yes	Yes	1067	Yes	440	448
24	L N G I V K	k	Yes	Yes	1031	Yes	455	473
25	S Z E P M J	u	No	No	1148	Yes	480	488
26	Q P W B T D	l	No	No	1563	Yes	495	513
27	V O H J C F	v	Yes	Yes	1170	Yes	520	528
28	U X L A U G	s	No	No	1855	Yes	535	553
29	R K I Y S N	z	No	No	1154	Yes	560	568
30	H W E Q M B	e	Yes	Yes	1193	Yes	575	593
31	Z P C G A X	g	Yes	Yes	970	Yes	600	608
32	D U Y N S I	t	No	No	1046	Yes	615	633

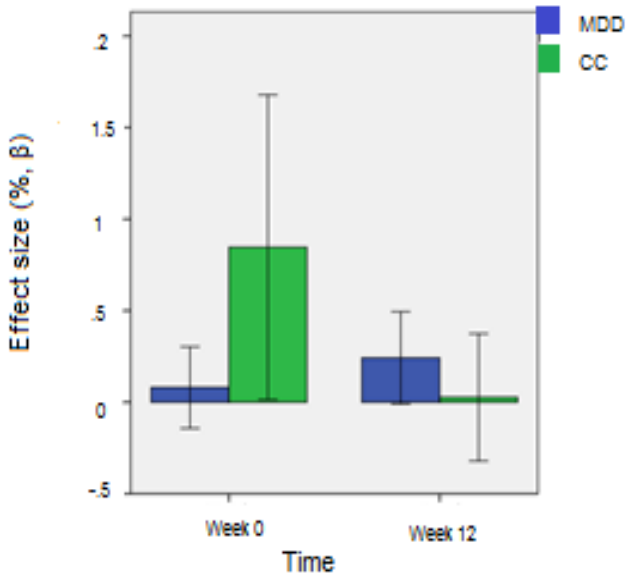
Table S3.2: Group by time interaction during delayed rehearsal phase.

Region (x,y,z coordinates)	Group	Mean fmri Activation		T	*P* value
		Week 0	Week 12		
Right Superior Temporal Pols	Patients	-0.710	0.148	-1.290	0.210
(46 16 -22)	Controls	0.568	-0.378	2.080	0.050
Left Middle Temporal Gyrus	Patients	0.091	0.254	-1.130	0.271
(-48 -2 -14)	Controls	0.847	0.027	1.535	0.141
Right Mid Cingulate Gyrus	Patients	0.019	0.014	0.119	0.907
(10 -26 34)	Controls	0.441	0.106	2.079	0.051
Left Middle Frontal Gyrus	Patients	-0.098	-0.053	-0.593	0.559
(-20 46 16)	Controls	0.461	0.018	2.024	0.057
Left Caudate	Patients	0.462	0.687	-1.632	0.117
(-8 -4 18)	Controls	1.870	0.938	2.270	0.035
Right Caudate	Patients	0.222	0.448	-1.480	0.153
(8 0 12)	Controls	1.757	0.974	2.158	0.044
Right Thalamus	Patients	0.133	0.554	-1.201	0.243
(12 -22 10)	Controls	0.245	0.138	1.686	0.108
Left Superior Temporal Gyrus	Patients	0.161	-0.073	2.483	0.021
(-58 -50 -12)	Controls	0.368	0.626	-1.270	0.219
Cerebellar Vermis	Patients	0.142	0.206	-0.587	0.563
(4 -52 -8)	Controls	0.715	0.206	2.988	0.008

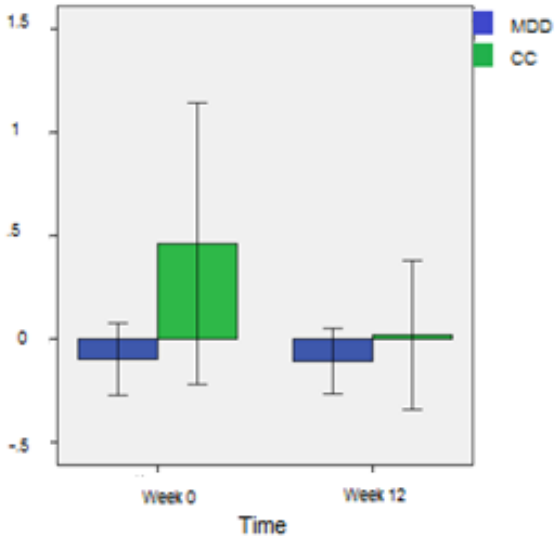
Figure S3.1: Group x time interaction during delayed rehearsal phase

The group by time interaction graphs for the remaining regions are displayed here. Effect sizes (β-weights) for the group by time interaction in the left middle temporal gyrus (x,y,z,= -48,-2, -14; $p_{(FWE\ corrected)}$ = 0.003), left middle frontal gyrus (x,y,z,= -20, 46, 16; $p_{(FWE\ corrected)}$ = 0.001), left superior temporal gyrus (x,y,z,= -58, -50, -12; $p_{(FWE\ corrected)}$ = 0.002) right cingulate gyrus (x,y,z, = 10,-26,34; $p_{(FWE\ corrected)}$ = 0.001), and right thalamus (x,y,z = 12,-22, 10; $p_{(FWE\ corrected)}$ =0.03).

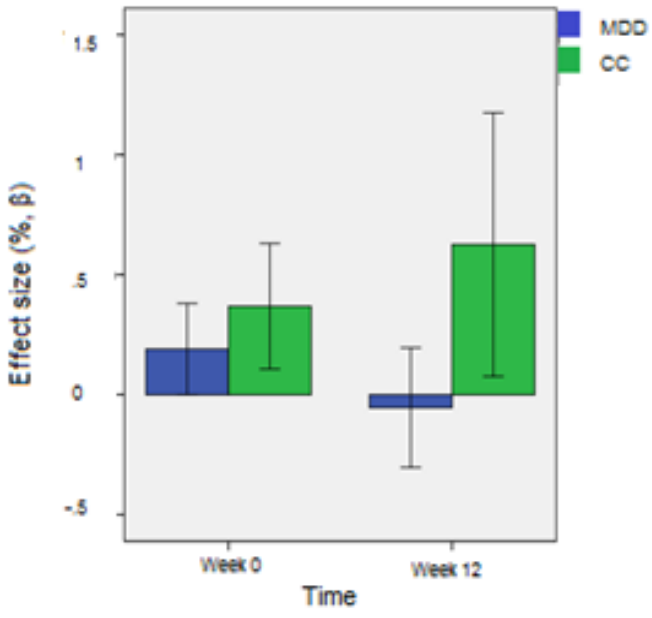
Left Middle Temporal Gyrus (x,y,z =-48, -2,-14)



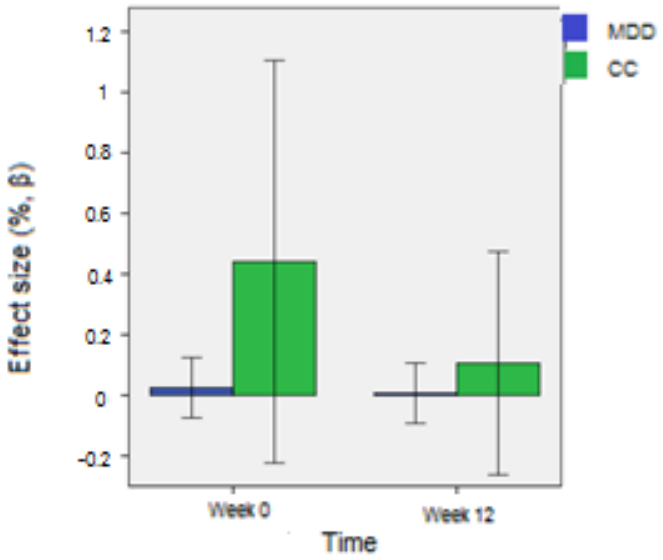
Left Middle Frontal Gyrus (x,y,z=-20,46,16)



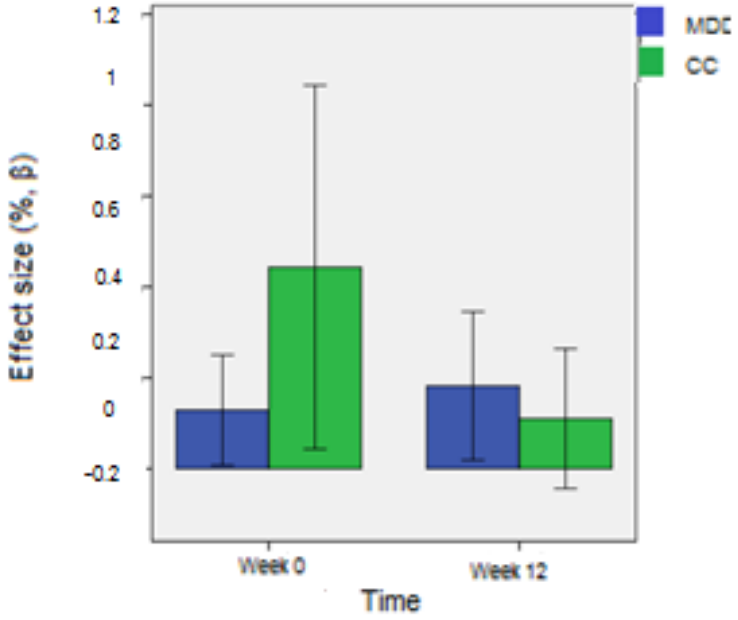
Left Superior Temporal Gyrus (x,y,z=-58,-50,-12)



Right Mid Cingulate Gyrus (x,y,z=10,-26,34)



Right Thalamus (x,y,z=12,-22,10)



Supplementary material 4

Published manuscripts (and in press)

Title:

Psychotherapy and antidepressant treatment effects on the functional neuroanatomy of depression

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Introduction

Major depressive disorder is a leading contributor to the global burden of disease and is regularly identified amongst the top five disabling conditions worldwide (Murray & Lopez, 2013). Depression is diagnosed by a prolonged lowering of mood or an inability to experience the usual feelings of pleasure which are associated with additional impairments in cognition, psychomotor functioning, and neurovegetative symptoms (American Psychiatric Association, 2013). The course of illness is typically characterised by recurrences and relapses, in which the risk of recurrence becomes more likely with an increasing number of previous episodes (Kessing, Hansen, Andersen, & Angst, 2004). It has been proposed that the processes mediating relapse grow progressively independent and are less linked to environmental stressors leading to a cycle of more frequently recurring episodes (Kendler, Thornton, & Gardner, 2000). Hence preventing relapse and recurrence is an essential feature of the clinical management of depression.

The neuropsychological biases and abnormalities evident in major depressive disorder (MDD) may be related to its onset and recurrences. In particular, MDD is associated with a negative affective bias in several neurocognitive domains. MDD patients show a greater recollection of negative information relative to healthy controls, such as words (Bradley, Mogg, & Williams, 1995) and facial expressions (Ridout, Astell, Reid, Glen, & O'Carroll, 2003). There is a selective attention towards negative stimuli in MDD (Beck, 2008), including towards negatively valenced words (Donaldson, Lam, & Mathews, 2007) and negative, mood-congruent images (Eizenman et al., 2003), and away from positive stimuli, such as happy facial expressions (Leppänen, 2006), which is particularly evident when the target stimuli is presented over a relatively long duration of time allowing more extensive processing (Mogg & Bradley, 2005). With facial expressions, MDD patients tend to misinterpret happy, neutral or ambiguous faces as being sad or less happy (Bourke,

Douglas, & Porter, 2010). The difficulties in discerning facial expressions have been purported to contribute to the interpersonal difficulties associated with MDD (Persad & Polivy, 1993). Moreover, the selective attentional bias towards negative facial expressions is evident even in recovered patients (Bhagwagar, Cowen, Goodwin, & Harmer, 2004; Joormann & Gotlib, 2007), while the induction of a mild negative mood in recovered patients can reinstate some of the negative biases observed in acutely depressed patients (Gemar, Segal, Sagrati, & Kennedy, 2001).

Both pharmacological and psychological treatments have demonstrated ameliorative effects on the negative emotional processing biases evident in depression. A 2-week treatment with citalopram and reboxetine enhanced recognition of emotions in MDD patients (Tranter et al., 2009), and a single dosage of citalopram normalised the bias towards fearful faces in MDD patients in remission (Bhagwagar et al., 2004). Even in healthy controls, a single dose of citalopram had improved their attention towards positive words though had also increased their recognition of fearful faces (Browning, Reid, Cowen, Goodwin, & Harmer, 2007). Likewise, cognitive bias modification techniques, involving positive interpretations of auditory stimuli using imagery, were associated with improvements in mood and cognitive biases in medication-free MDD patients (Blackwell & Holmes, 2010). Furthermore, enhancement of the recognition of happy faces following antidepressant treatment was linked with improvements in symptoms, wellbeing and social functioning (Tranter et al., 2009), indicating the potential for pharmacological as well as neuropsychological modulation of the negative biases rather than their being persistent, trait-related features of MDD.

Functional magnetic resonance imaging (fMRI) studies have applied various experimental paradigms in order to delineate the networks underlying the affective biases and cognitive impairments in MDD (Frodl et al., 2009; Lawrence et al., 2004; Mitterschiffthaler et al., 2008; Surguladze et al., 2005; Wagner et al., 2006). In order to distinguish state-specific from trait-related neural features, it is important to consider the depressive state of the MDD sample (ex. acute depressive episode, in recovery, or in remission) and whether the sample consists

of a cross sectional analysis of MDD subjects in a variety of states or whether the study is a longitudinal investigation of the same MDD patients following a variety of treatments. For example, fMRI studies have investigated impairments during an acute depressive episode (Grimm et al., 2008; Harvey et al., 2005; Mitterschiffthaler et al., 2008) as well as the changes following treatment (Arnone et al., 2012; Fu et al., 2007; Fu et al., 2004; Fu, Williams, et al., 2008; Sheline et al., 2001; Victor, Furey, Fromm, Öhman, & Drevets, 2010; Walsh et al., 2007). The majority of studies have examined the effects of pharmacological treatments (Arnone et al., 2012; Davidson, Irwin, Anderle, & Kalin, 2003; Fu et al., 2007; Fu et al., 2004; López-Solà et al., 2010; Rosenblau et al., 2012; Sheline et al., 2001; Stoy et al., 2012; Victor et al., 2010; Walsh et al., 2007), while there have been fewer studies of psychological interventions (Buchheim et al., 2012; Dichter et al., 2009; Dichter, Felder, & Smoski, 2010; Fu, Williams, et al., 2008; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Yoshimura et al., 2014)**.**

Longitudinal fMRI studies investigating affective processing have commonly used standardized series of facial expressions (ex. Ekman & Friesen, 1976) or pictures (ex. International Affective Picture System (IAPS); Lang, Bradley, & Cuthbert, 1999). The emotional processing tasks applied in longitudinal fMRI studies may be considered to be engaging predominantly implicit or explicit processing. For example, in a task involving the presentation of emotional faces, the explicit instruction may be to identify the gender of the presented face while the emotional expression is processed implicitly, or the explicit instruction may be to identify the emotion expressed by the presented face which becomes an explicit processing of the emotion. Implicit affective processing tasks are often used in neuroimaging studies because they are associated with greater probability of engaging key limbic regions within the MDD network, such as the amygdala (Costafreda, Brammer, David, & Fu, 2008). The majority of the longitudinal MDD studies have focussed on the functional correlates of treatment in response to emotional processing (Arnone et al., 2012; Davidson et al., 2003; Fu et al., 2007; Fu et al., 2004; Fu, Williams, et al., 2008; Ritchey et al., 2011;

Victor et al., 2010). Other emotional processes, such as reward (Dichter et al., 2009; Stoy et al., 2012) and painful stimuli (López-Solà et al., 2010), as well as cognitive processes, such as verbal working memory (Walsh et al., 2007) and cognitive control (Wagner et al., 2010), have also been investigated.

In the present review, we discuss the functional neural correlates of the effects of pharmacotherapy as well as psychological therapy in MDD. We also provide an overview of predictors of clinical response and the potential to develop neuroimaging-based biomarkers.

Antidepressant treatment effects on regional brain activations

Healthy emotional regulation depends on the interplay between frontal and limbic regions. A frequently applied strategy of emotion regulation involves reinterpreting the meaning of a situation in order to reduce the affective impact, which may be termed cognitive reappraisal (Gross, 2002). The neural correlates of the process of reappraisal involve cognitive control regions within the prefrontal cortex and modulation of emotion-related activity in the amygdala (Buhle et al., 2013). The amygdala plays a key role in processing of emotional stimuli, both negative and positive, although there is a higher probability of amygdala responsivity to stimuli which evoke fear and disgust relative to those which give rise to happiness (Costafreda et al., 2008). Studies of the neural correlates of emotional processing in MDD have demonstrated increased amygdala activation during an acute depressive episode as compared to controls in response to a variety of negative stimuli, such as sad faces (Arnone et al., 2012; Fu et al., 2004; Victor et al., 2010), fearful or angry faces (Ruhe, Booij, Veltman, Michel, & Schene, 2012; Sheline et al., 2001), and negatively valenced pictures (Anand et al., 2005; Rosenblau et al., 2012). Following treatment, subsequent normalisation of this increase in amygdala activation has been widely observed (Arnone et al., 2012; Fu et al., 2004; Rosenblau et al., 2012; Sheline et al., 2001).

These treatment studies have examined selective serotonin reuptake inhibitor (SSRI) class of antidepressant medications, such as sertraline (Anand, Li, Wang, Gardner, & Lowe, 2007;

Sheline et al., 2001; Victor et al., 2010), fluoxetine (Fu et al., 2004), citalopram (Arnone et al., 2012), and escitalopram (Rosenblau et al., 2012). Normalization of amygdala activity in patients following antidepressant treatment could reflect improvements in depression severity as well as, or alternatively, could be evidence of the effects of SSRI treatment on amygdala responses. The mechanism may be consistent with the density of serotonin receptors within the amygdala (Xu & Pandey, 2000) which are a target of action for SSRIs (X. Jiang, Chen, Smerin, Zhang, & Li, 2011). Short term administration of SSRIs in both healthy volunteers (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006) and MDD patients (Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012) had normalized amygdala responses to negative emotional stimuli, which preceded the clinical improvements (Godlewska et al., 2012), suggesting a therapeutic mechanism of SSRI treatment for MDD. The effects of antidepressants with more prominent noradrenergic mechanisms require further investigation as noradrenergic reuptake inhibitors may modulate the attentional regulation of emotional processing which are mediated by medial and prefrontal regions (Fu et al., 2001; Outhred et al., 2013).

Functional MRI studies have examined amygdala activity in MDD patients in remission in order to delineate whether the observed response is a state- or trait-related feature. In remitted MDD patients relative to controls, no significant differences in their amygdala activation during processing of sad, fearful or happy facial expressions have been reported (Arnone et al., 2012), suggesting that increased amygdala activation may be a state-dependent marker in depression. However, in response to masked faces, remitted MDD patients relative to controls did show elevated amygdala activity during masked sad facial processing, with a pattern of activations similar to acutely depressed patients (Victor et al., 2010). Although there is clear support for normalisation of amygdala activation following antidepressant treatment, the findings have not been wholly consistent. It is also important to note the factors which affect the probability of amygdala response, including valence and form of presentation, as well as the type of analysis, as a region of interest (ROI) approach

(Arnone et al., 2012; Rosenblau et al., 2012; Sheline et al., 2001) provides greater power to detect a difference relative to whole brain analyses (Costafreda et al., 2008).

Antidepressant treatment has also been associated with an attenuation of activation in a wide distribution of limbic and subcortical regions that are dysregulated in MDD, reflecting impairments in associated neurocognitive functions, including in the dorsal anterior cingulate which is involved in conflict monitoring and cognitive control (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Mitterschiffthaler et al., 2008), orbitofrontal cortex in reward processing (Rolls, 2000), and hippocampus in memory processing (Burgess, Maguire, & O'Keefe, 2002). Acutely depressed MDD patients have shown increased activation in the anterior cingulate (Fu et al., 2004), insula (Fu et al., 2004), hippocampus (Victor et al., 2010) and putamen (Fu et al., 2004; Surguladze et al., 2005) during implicit processing of sad faces relative to controls, which was attenuated following pharmacological therapy (anterior cingulate: Fu et al., 2004; Victor, Furey, Fromm, Öhman, & Drevets, 2013; insula: Fu et al., 2004; putamen: Fu et al., 2004). In response to negative pictures, MDD patients similarly showed a normalisation of activation in the orbitofrontal and dorsolateral prefrontal cortices (Rosenblau et al., 2012), and in subcortical regions, including striatum (Anand et al., 2007). Antidepressants appear to promote a normalisation of activations within a network of limbic and subcortical regions which show increased responsivity to negative affective stimuli during an acute depressive episode. Furthermore, a strong association between cortico-limbic activations and clinical improvements has been observed, such that the patients who showed the most improvement also had the greatest reductions in activation with treatment (Fu et al., 2004).

In response to positive facial expressions, the negative bias observed in MDD patients (Bourke et al., 2010) has also been linked to impairments in limbic and subcortical regions. Implicit processing of happy facial expressions in MDD patients relative to healthy controls has been associated with reduced activation in the amygdala and parahippocamapal regions (Lawrence et al., 2004), as well as in the posterior cingulate, precuneus, lingual gyri, and

cerebellum, which improved following antidepressant treatment (Fu et al., 2007). Happy facial expressions have also been associated with increased activations in the fusiform gyrus in MDD patients following treatment (W. Jiang et al., 2012). Fusiform responses are greater for attended faces (Pizzagalli et al., 2002), and MDD patients show greater fusiform activation than controls when attending to negative emotional stimuli (versus a neutral baseline) but decreased fusiform responses during attentional processing of positive emotions (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013). These findings outline the functional network underlying the neurocognitive observations that MDD patients are more likely to attend to faces of increasing sadness in comparison to healthy controls (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007), who in turn attend more to happy facial expressions (Joormann & Gotlib, 2007), and suggest that antidepressant treatment may normalise the impairments.

Antidepressants have additionally demonstrated regulation of impaired activations in prefrontal cortical regions which have been associated with more cognitive demands. Using variations of the Stroop task to investigate neural correlates of executive control of attention, increases in rostral anterior cingulate (Mitterschiffthaler et al., 2008; Wagner et al., 2006), dorsolateral prefrontal (Wagner et al., 2006), as well as decreases in the precuenus, posterior cingulate, and occipital regions (Kikuchi et al., 2012) have been observed in acutely depressed MDD patients relative to controls. Mitterschiffthaler et al. (2008) had used a variant of the Stroop which employed affective words, and Wagner et al. (2006) had presented the response as an option along with the target word to reduce memory demand. Modifications of the task were also made to accommodate the parameters of fMRI scanning including a button press response instead of vocalisation (Wagner et al., 2006; Kikuchi et al., 2012), though Mitterschiffthaler et al. (2008) used a clustered fMRI acquisition sequence in order to allow overt verbal responses. The effects of antidepressant treatment were attenuation of activations in the prefrontal, amygdala-hippocampal, and parietal regions in

MDD patients (Wagner et al., 2010), further support the normalisation of cortico-limbic regional activations by antidepressant therapy.

However, it is important to consider the factors which may contribute to the observed effects, including effects due to the form of treatment, ie. antidepressant treatment and potentially related to the specific class of antidepressant, to improvements in depressive symptoms, as well as to repeated performance of the tasks and scans. In order to account for potential effects of time and repeated neuroimaging scans, studies have included healthy volunteers who had the same scans at the same time points as the MDD patients (ex. Davidson et al., 2003; Fu et al., 2004; López-Solà et al., 2010; Rosenblau et al., 2012; Stoy et al., 2012; Walsh et al., 2007), while others have not performed follow up scans on healthy control subjects, instead included only a single scan, usually done at the time of study entry (ex. Wagner et al., 2010; Wang et al., 2012). The inclusion of a control group though bears added costs and the risk of subjects being unable to return for serial scans. The addition of a MDD treatment arm with a placebo form of treatment would help to account for potential placebo-related effects and state-related changes. A limited number of PET studies have examined the functional correlates of placebo effect in depression (ex. Mayberg et al., 1999; Mayberg et al., 2002), but to our knowledge, there have not been any longitudinal fMRI studies which have included a MDD patient group receiving a placebo treatment.

Pharmacological treatment effects on neural connectivity

In order to examine the relationship between regions, a connectivity analysis attempts to define the interaction between brain regions, which could potentially be excessively engaged, impaired or even unaltered in MDD. The amygdala has connections with the subgenual anterior cingulate and receives connections from dorsal cingulate cortex (Aggleton & Saunders, 2000). Reduced frontocortical and limbic regional connectivity has been observed in MDD (Anand et al., 2005; Chen, Suckling, et al., 2007; Costafreda et al., 2013) which may worsen with increasing severity of depression (Friedel et al., 2009;

Matthews, Strigo, Simmons, Yang, & Paulus, 2008) and improve following antidepressant treatment (Chen, Suckling, et al., 2007). Activation of the lateral prefrontal and dorsal cingulate cortices suppresses amygdala activation, part of the process of voluntary emotional down-regulation (Carballedo et al., 2011; Costafreda et al., 2008). These findings indicate that depression is associated with impairments in the inhibitory influence of cortical regions on limbic regions, which may be ameliorated by treatment.

Neural effects of psychological therapy

Fewer studies to date have investigated the neural correlates of psychological therapy. These studies have examined a variety of states and tasks, such as resting state (Brody et al., 2001; Goldapple et al., 2004; Martin, Martin, Rai, Richardson, & Royall, 2001), dysfunctional attitudes (Sankar et al., in press), cognitive control (Dichter et al., 2010), facial expressions (Fu, Williams, et al., 2008; Ritchey et al., 2011), and reward processing (Dichter et al., 2009), using positron emission tomography (PET) (Brody et al., 2001; Goldapple et al., 2004; Kennedy et al., 2007), single-photon emission computed tomography (SPECT) (Martin et al., 2001), and functional MRI (Buchheim et al., 2012; Dichter et al., 2010; Fu, Williams, et al., 2008; Ritchey et al., 2011).

Increases in baseline activations in the amygdala-hippocampal regions in MDD patients relative to healthy controls have been followed by significant reductions following treatment with cognitive behavioural therapy (CBT) (Fu, Williams, et al., 2008) as well as with psychodynamic psychotherapy (Buchheim et al., 2012). Increases within the prefrontal regions in MDD patients, such as the medial prefrontal (Buchheim et al., 2012; Yoshimura et al., 2014), orbitofrontal (Dichter et al., 2010), dorsolateral and ventrolateral prefrontal cortices (Brody et al., 2001) also normalized following a variety of forms of psychological treatments, including CBT (Yoshimura et al., 2014), behavioural activation therapy (Dichter et al., 2010), interpersonal psychotherapy (IPT) (Brody et al., 2001) and psychodynamic psychotherapy (Buchheim et al., 2012). In the anterior cingulate, several studies have

demonstrated increased activation (Dichter et al., 2009; Fu, Williams, et al., 2008; Goldapple et al., 2004) but there have also been reports of decreases (Brody et al., 2001; Buchheim et al., 2012) in activation following psychological therapy.

Investigations of the differential effects of pharmacological and psychological therapies on regional brain activity have compared CBT (Goldapple et al., 2004; Kennedy et al., 2007) or IPT (Brody et al., 2001; Martin et al., 2001) with antidepressant medications, such as paroxetine (Brody et al., 2001; Goldapple et al., 2004) and venlafaxine (Kennedy et al., 2007; Martin et al., 2001). MDD patients in an acute episode were assigned randomly to either psychological therapy or pharmacological intervention (Kennedy et al., 2007; Martin et al., 2001), and few studies used a nonrandomized design, in which treatment type was guided by patient preference (Martin et al., 2001) or CBT treatment group were compared post-hoc to an independent group of paroxetine responders (Goldapple et al., 2004). Both antidepressant treatment and psychotherapy were associated with reductions in the prefrontal cortex, including the middle frontal (Brody et al., 2001), lateral orbitofrontal, dorsomedial (Kennedy et al., 2007) and ventral prefrontal (Goldapple et al., 2004) regions, as well as increases in the basal ganglia (Martin et al., 2001), temporal lobe (Brody et al., 2001) and lateral inferior occipital region (Kennedy et al., 2007). Antidepressants were specifically associated with decreases in limbic regions, such as the insula (Goldapple et al., 2004), posterior (Kennedy et al., 2007) and ventral (Goldapple et al., 2004) subgenual cingulate regions, as well as increases in the posterior temporal lobe (Martin et al., 2001), brainstem and cerebellum (Goldapple et al., 2004). Psychological therapies, on the other hand were associated with decreases in the thalamus (Kennedy et al., 2007), and in the prefrontal cortex, including orbitofrontal, medial and ventrolateral regions (Goldapple et al., 2004), as well as increases in the subgenual (Kennedy et al., 2007) and dorsal (Goldapple et al., 2004) cingulate regions. In the posterior cingulate region, however, there have been findings of both decreases (Goldapple et al., 2004) and increases (Martin et al., 2001) in activations following psychological therapy.

It has been proposed that cognitive therapy shows a cortical “top-down” mechanism of action, as it focuses on altering memory and attention processes that are involved in the mediation of cognitive biases and maladaptive processing of information (DeRubeis, Siegle, & Hollon, 2008). There is growing evidence though to suggest that antidepressants may also show a similar mechanism of action to cognitive therapy whereby antidepressant modulate the negative biases and memory impairments in depression very early on in the course of treatment, even before patients report any change in their mood or anxiety (Harmer, Goodwin, & Cowen, 2009; Harmer, O’Sullivan, et al., 2009). The common neural mechanisms of action of antidepressants and cognitive therapy may reflect their targeting similar underlying processes that lead to improvements in depressive symptoms. The number of studies have been limited to date though, along with variations with respect to treatment, treatment duration, and task processing, as well as effects of improvements in symptom severity which must also be considered.

Functional neuroimaging predictors of clinical response

At the present time, the diagnosis of depression is based solely on clinical signs and symptoms, and there are no biological tests that are used to diagnose the disorder or to predict clinical response to a particular treatment or the course of the illness. Building on investigations of the neural treatment effects in major depression, studies have also sought to identify the neural biomarkers that predict clinical response before initiation of treatment or early in the course of treatment. Meta-analysis of pharmacological and psychotherapy treatment studies showed that increased baseline activity in the anterior cingulate, medial prefrontal and orbitofrontal regions was predictive of a better response to treatment, whilst activity in the right striatum and anterior insula was predictive of a poorer prognosis (Fu, Steiner, & Costafreda, 2013). Increased anterior cingulate activity as being predictive of response to antidepressant medications, prior to the initiation of treatment, has been highly replicated, while the direction of the prediction for CBT has been more mixed (Fu et al.,

2013). Elicitation of anterior cingulate in response prediction has been observed with numerous tasks, including resting state PET studies (Kennedy et al., 2007; Mayberg et al., 1997) and with both cognitive (Marquand, Mourão-Miranda, Brammer, Cleare, & Fu, 2008; Roy et al., 2010) and emotional processing (Chen, Ridler, et al., 2007; Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Davidson et al., 2003; Keedwell et al., 2010) fMRI tasks. There have been as well some notable inconsistencies as some reports have indicated that greater anterior cingulate activity was predictive of a poorer clinical response to pharmacotherapy (Brody et al., 1999; Konarski et al., 2009) as well as to CBT (Konarski et al., 2009; Siegle, Carter, & Thase, 2006). Increased anterior cingulate activity may indicate greater responsivity to reward processing (Rogers et al., 2004) and in turn predict a better clinical response. The insula is engaged by negative emotional stimuli (Anand et al., 2005; Van Dillen, Heslenfeld, & Koole, 2009), in particular the anterior region for social stimuli with interoceptive integration of internal and external stimuli of emotional pain recognition (Singer et al., 2004). More recently, baseline hypometabolic activity in the insula was associated with remission to CBT and poor response to escitalopram, whilst the opposite effect was seen with insula hypermetabolism (McGrath et al., 2013).

For these findings to be applicable in clinical settings, it is important to identify diagnostic and prognostic markers with high predictive accuracy at the individual level (Fu & Costafreda, 2013). It is possible to apply methods of analysis to neuroimaging measures in order to determine what would be expected for a particular individual along with a measure of how likely that outcome may be (Nouretdinov et al., 2011). One set of analysis methods is machine learning, such as support vector machine (SVM) (Fu, Mourao-Miranda, et al., 2008). For example, we found that baseline neural activity during sad facial processing predicted remission to CBT with a sensitivity of 71 % and a specificity of 86% for individual patients (Costafreda et al., 2009). Future research should also aim to investigate whether integration of neuroimaging biomarkers based on multiple neural processes associated with depression (ex. affective and emotional processing and structural neuroimaging) would

achieve more accurate classification. The investigation of neuroimaging data using pattern based classification methods to obtain clinically useful biomarkers with high predictive accuracy at the individual level would help to optimize treatment strategies at an early stage. This would be of particular benefit for patients whose illnesses may be less likely to improve solely with conventional treatment methods and who would benefit from an earlier initiation of alternative or combination therapies.

Conclusions

In summary, research has begun to elucidate the function of antidepressants and psychotherapy in modulating the regions involved in the emotional, cognitive and behavioural disturbances that underlie major depression. Further placebo-controlled longitudinal fMRI studies would assist in distinguishing between the effects of treatment and changes associated with depressive state and to control for effects of time and test-retest with particular neuroimaging paradigms. Additional investigations are also required to determine the common and distinct mechanisms of action of antidepressants and psychological therapies. Pattern classification based analysis of neuroimaging data is beginning to delineate potential biomarkers for both diagnosis and prognosis with high predictive accuracy at the individual level which will aid in the development of clinically useful measures.

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Mood Disorders (AH Young, Section Editor)

Recent Advances in Neuroimaging of Mood Disorders: Structural and Functional Neural Correlates of Depression, Changes with Therapy, and Potential for Clinical Biomarkers

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Opinion Statement

Major depressive disorder (MDD) is associated with key regions of the brain involved in emotional processing. The present meta-analysis revealed widespread structural reductions in limbic and prefrontal regions that occur in MDD, with no regions of increased grey matter volume. Functional impairments involve many of the same regions with dysregulated interactions between limbic and cortical structures. Longitudinal treatment studies have predominantly investigated pharmacological therapies, and there have been fewer studies of psychological treatments. Reports of increased hippocampal

volume and reductions in amygdala activation following treatment suggest implications for the course of illness and the impact of pharmacological as well as psychological therapies. Measures of regional brain volume and activity during an acute depressive episode prior to or early in the course of treatment offer the potential to develop predictors of clinical response. High predictive accuracy at the level of the individual is essential for translation of these findings to clinical use. Development of such biomarkers may help to guide treatment strategies, particularly for individuals who may not benefit from current first-line therapeutic options, in order to preclude a potential series of ineffective treatment trials.

Introduction

Major depression is one of the top contributors to the global burden of disease [1, 2]. It is an often debilitating disorder that typically follows a recurring and relapsing course of illness. At present, the diagnostic criteria of depression include an assessment of mood as well as cognitive and somatic symptoms, and treatment decisions are based on clinical characteristics such as severity and course of the illness as well as past treatment response. Evidence-based treatments for depression include antidepressant medications and psychological therapies, individually or in combination, but remission rates have been relatively modest [3]. To date, there are no biological markers that are used in clinical practice to diagnose the disorder or to predict treatment response [4••, 5•].

Structural and functional magnetic resonance imaging (MRI) studies have sought to delineate the brain abnormalities associated with depression and to examine the effects of treatment. Understanding the neurobiological mechanisms that contribute to the pathogenesis of the disorder may also provide models in the development of biomarkers for diagnosis, prognosis, and response prediction [5•]. Often, fMRI studies in depression have used experimental paradigms such as tasks of affective and cognitive processing to engage the regions that may be impaired. Connectivity analyses provide an additional understanding of the interactions among brain regions. Longitudinal treatment studies have predominantly focussed on antidepressant treatment, and selective serotonin reuptake inhibitors (SSRIs) in particular, while there have been fewer studies of psychological treatments [6••]. Identifying neurobiological correlates of treatment response and establishing biological markers of diagnosis and response prediction will require high predictive accuracy at the individual level as well as a measure of the confidence of the prediction [7]. In this way, treatment strategies could be personalised, in particular to identify patients with more severe forms of the disorder early in the course of their illness in order to prevent a potential series of ineffective treatment trials.

Structural and Functional Neural Correlates of Depression

MRI studies have revealed structural and functional brain abnormalities associated with MDD in limbic and prefrontal regions, key areas involved in emotional processing and regulation. In our meta-analysis of grey matter abnormalities in MDD, we retrieved 34 studies from a systematic literature search of five databases (PubMed, Scopus, Ovid MEDLINE, PsycINFO, and Ovid EMBASE) between January 1995 and June 2012 [8](Table 1). The subjects included a total of 1,341 MDD patients and 1,364 healthy controls. The patient group comprised adults who were both on medication and not taking medication. Neuroimaging studies utilizing region-of-interest (ROI) as well as voxel-based morphometry (VBM) methods were included in order to determine to what extent the methods used in individual studies may have

influenced the results of the meta-analysis. Studies that reported no significant difference in grey matter volume (GMV) or density between patients and control subjects were also included.

The whole-brain analysis revealed volumetric reductions of grey matter in 10 clusters across the brain comprising the right anterior cingulate cortex (ACC), right medial superior frontal gyrus, right dorsolateral prefrontal cortex (DLPFC), bilateral orbitomedial prefrontal cortex, right inferior frontal gyrus opercular part and triangular part, bilateral insula, right claustrum, and the right putamen.

The combined whole-brain and ROI analysis revealed more extensive grey matter reductions across 18 clusters, including the bilateral anterior cingulate, bilateral medial superior frontal gyrus, right DLPFC, left superior frontal gyrus, right inferior frontal gyrus opercular part, bilateral inferior frontal gyrus triangular part, bilateral insula, right claustrum, and right rectus gyrus, in MDD patients compared to controls. In addition to the whole-brain findings, grey matter reductions were also significant in the bilateral parahippocampal gyrus, left thalamus, and left postcentral gyrus. Notably, there was no increased grey matter volume found in any region in either the whole-brain or combined whole-brain and ROI analyses.

The ACC is a region consistently implicated throughout the course of MDD. Structural magnetic resonance imaging (sMRI) studies have demonstrated total volume reductions present in the ACC in never-treated MDD patients [9, 10]. Studies of medication-naïve and medication-free samples may provide further elucidation of brain abnormalities more directly related to MDD itself, without potentially confounding effects of medication. Voxel-based morphometry (VBM) analysis of sMRI data have shown that ACC grey matter density is significantly reduced in medication-free and medication-naïve patients [11–13]. Reduced white matter volumes have also been reported in the right ACC [14].

There is evidence that such structural abnormalities have functional consequences likely related to impairments in emotional processing [15]. For example, increased activity of the ACC as well as in the amygdala, anteromedial prefrontal cortex, parahippocampus, and insula regions in response to negative images has been observed in unmedicated depressed patients [16], and altered functional connectivity has been reported in subgenual ACC networks of medication-naïve MDD adolescents when evaluating negative emotional stimuli [17]. MDD is associated with dysregulated interconnections within limbic–cortical structures, particularly between the ACC and amygdala [18, 19].

In the amygdala, reduced volumes have been reported in both region-of-interest [20] and VBM [11, 21] studies. Functional activation tasks have demonstrated abnormal and greater amygdala response to negative emotion in MDD patients at baseline prior to antidepressant treatment as compared to controls [4••, 16, 22–24]. Studies have revealed decreased functional connectivity between the amygdala and PFC, including the ACC, in response to negative emotional stimuli [19, 25], and the amygdala and left anterior insula networks in whole-brain resting-state studies of medication-naïve MDD [26]. It is clear that MDD modulates amygdala responsivity and widespread functional connectivity to prefrontal cortical regions [19].

Table 1. Demographic summary of studies included in meta-analysis [8]

Study	Patients		Healthy controls		Depression rating scale (score)	Medication status	Illness duration	Anxiety disorder	Matching	Tesla
	N (m/f)	Age mean±SD	N (m/f)	Age mean ±SD						
Abe et al. (2010) [93]	21 (11/10)	48.1 (13.5)	42 (22/20)	48 (13.2)	17-HDRS =9.2	19/21 on AD; 2/21 Medication-free	-	Not excluded	Age, gender	1.5
Amico et al. (2011) [14]	33 (19/14)	32 (8)	94 (53/41)	30.55 (8.15)	21-HDRS =23	27/33 on AD; 6/33 Medication-free	3.4 years	Excluded	-	1.5
Avila et al. (2011) [94]	48 (14/34)	70.04 (6.67)	31 (8/23)	70.29 (7.24	HDRS =18.58	8/48 on AD	-	Not excluded	Age	1.5
Bergouignan et al. (2009) [95]	21 (4/17)	33.16 (9.58)	21 (7/14)	28.21 (5.5)	MADRS= 28.71 / BDI= 19.36	21/21 on AD	8.45 years	Not excluded	Age, level of education	1.5
Cheng et al. (2010) [96]	68 (21/47)	29.91 (7.92)	68 (21/47)	30.54 (7.3)	17-HDRS= 22.32	68/68 Medication-free	10.98 months	Excluded	Sex, age, education	1.5
Egger et al. (2008) [97]	14 (4/10)	71.4 (7.49)	20 (7/13)	72.3 (7.77)	GDS=21.14	10/14 on AD	-	-	Sex, age, education	1.5
Frodl et al. (2008) [98]	77 (42/35)	46.1 (11.3)	77 (42/35)	43.6 (11.3)	21-HDRS= 22.8	61/77 on AD; 16/77 Medication-free	5.4 years	Excluded	Age, gender, handedness	1.5
Hwang et al. (2010) [99]	70 (70/0)	79.4 (5.3)	26 (26/0)	79.5 (4.3)	HDRS=29.2	-	Suicidal depressive 6.5 months Non-suicidal depressive 9.5 months	-	Age and education	2
Inkster et al. (2010) [100]	145 (51/94)	49 (13.3)	183 (73/ 110)	48 (13.3)	SCAN=5.5	119/145 on AD, last 6 months	14.3 months	Not excluded	Age, gender, ethnicity	1.5
Kim et al. (2008) [101]	22 (0/22)	38.5 (9.7)	25 (0/25)	35.3 (11.25)	BDI=22.3	10/22 on AD; 12/22 Medication-free	-	Excluded	Age, education	1.5
Koolschijn et al. (2010) [102]	28 (0/28)	64.04 (10.9)	38 (0/38)	61.89 (11.03)	MADRS =18.3	17/28 on AD	31 years	Excluded	Age, gender, handedness, education, health status	1.5
Lai et al. (2010) [12]	16 (5/11)	37.91 (8.76)	15 (4/11)	34.3 (9.87)	HDRS =35.91	16/16 Medication-naïve	17.5 weeks	Not excluded	Age, sex, handedness	3
Lee et al. (2011) [103]	47 (5/42)	46 (9.1)	51 (5/46)	45.7 (8.04)	17-HDRS =20.1	29/47 on AD 18/47 Medication-naïve	46.7 months	Excluded	-	1.5
Leung et al. (2009) [104]	17 (0/17)	45.5 (8.5)	17 (0/17)	45.8 (9.8)	BDI=29.7	17/17 on AD	7 years	Excluded	Age, intelligence	1.5
Li et al. (2010) [105]	44 (11/33)	44.5 (11.7)	25 (6/19)	40.6 (12.7)	17-HDRS =21.9	44/44 on AD	Non-Remitting MDD 9.4 years; Remitting MDD 9 years	Not excluded	Age, gender, handedness	1.5

Table 1. (Continued)

Study	Patients N (m/f)	Age mean ± SD	Healthy controls N (m/f)	Age mean ± SD	Depression rating scale (score)	Medication status	Illness duration	Anxiety disorder	Matching	Tesla
Mak et al. (2009) [106]	17 (0/17)	45.5 (8.5)	17 (0/17)	45.8 (9.8)	BDI=29.7	17/17 on AD	-	Excluded	Age, intelligence	1.5
Mwangi et al. (2012) [107]	30 (11/19)	45.4 (11.25)	32 (14/18)	41.8 (11.75)	BDI=30.45 / HDRS= 25.54	25/30 on AD 5/30 Medication-free	>3 months	Not excluded	Age, gender, intelligence	1.5
Peng et al. (2011) [28]	22 (8/14)	46.7 (8.9)	30 (11/19)	45.9 (9)	17-HDRS= 18.5	5/22 on AD	8.6 months	Excluded	Age, gender, education	3
Pizzagalli et al. (2004) [108]	38 (15/23)	34.8 (10.85)	18 (8/10)	38.1 (13.6)	HDRS=19.15	38/38 Medication-free, 2 months	-	Not excluded	-	1.5
Ries et al. (2009) [109]	15 (5/10)	66.3 (5.3)	32 (14/18)	68.4 (7.4)	CES-D = >10	-	-	Excluded	Age, gender	3
Salvadore 2et al. (2011) [29]	Currently depressed 58 (21/37) Remitted 27 (6/21)	Currently depressed 38.8 (11.1) Remitted 40.2 (12.2)	107 (47/60)	36.2 (10.3)	MADRS Currently depressed = 26	58/58 Medication-free	Currently depressed 18.4 years Currently remitted 15.1 years	Excluded	-	3
Scheuerecker et al. (2010) [35]	13 (10/3)	37.9 (10.1)	15 (10/5)	35.5 (10.9)	HDRS =20.5	13/13 Medication free	52.3 months	Excluded	Age, sex, handedness	3
Shah et al. (1998) [110]	TRD 20 (13/7) Remitted 20 (13/7)	TRD 48.9 (9.8) Remitted 47.7 (9.9)	20 (13/7)	49.3 (11.8)	17-HDRS TRD=20.6	20/20 on AD	TRD 263 weeks Remitted 76 weeks	Excluded	Age, gender, intelligence, education	1
Soriano-Mas et al. (2011) [111]	70 (29/41)	61.56 (9.68)	40 (17/23)	59.23 (7.09)	17-HDRS =28.6	50/70 on AD 20/70 Medication-free	10.45 years	Excluded	-	1.5
Tang et al. (2007) [11]	14 (0/14)	29.5 (6.84)	13 (0/13)	29.46 (6.86)	17-HDRS = >18	14/14 Medication-free	-	Not excluded	Age, education, family history	1.5
Treadway et al. (2009) [112]	19 (9/10)	35.2 (10.5)	19 (9/10)	30.3 (8.6)	HDRS =21.5	19/19 Medication-free	12.9 years	Not excluded	Age and gender	3
Taki et al. (2005) [113]	34 (13/21)	72.37 (1.7)	109 (55/54)	72.17 (1.73)	GDS=18.6	34/34 Medication-free	-	Not excluded	Age	0.5
VanTol et al. (2010) [114]	68 (24/44)	37.16 (10.24)	65 (24/41)	40.54 (9.71)	MADRS =13.1	58/156 on AD	13 months	Not excluded	Age, sex, handedness	3
Vasic et al. (2008) [115]	15 (9/6)	37.4 (8.5)	14 (8/6)	31.4 (9.6)	21-HDRS= 16.9	15/15 on AD	43.4 months	Excluded	Age, handedness, education and intelligence	1.5
Wagner et al. (2008) [27]	15 (0/15)	41.4 (9.2)	16 (0/16)	38.8 (9.1)	HDRS=23.5	15/15 Medication-free, 1 week prior	7.5 months	Excluded	Age and education	1.5
Wagner et al.	30 (5/25)	37.55 (11.5)	30 (5/25)	35.1 (10.4)	21-HDRS High	-	High risk suicide	Excluded	Gender, age and	1.5

Table 1. (Continued)

Study	Patients N (m/f)	Age mean±SD	Healthy controls N (m/f)	Age mean ±SD	Depression rating scale (score)	Medication status	Illness duration	Anxiety disorder	Matching	Tesla
(2011) [116]					risk suicide = 23.9 Non-high-risk suicide = 25.7		8.9 years Non-high risk suicide 3 years		education	
Yuan et al. (2008) [117]	19 (9/10)	67.1 (7.2)	16 (8/8)	67.7 (3.8)	HDRS =3.1	19/19 Medication-free, 3 months prior	3.7 years	Excluded	Age	1.5
Zhang et al. (2009) [118]	15 (10/5)	33.5 (10.2)	15 (10/5)	33.4 (10.2)	17-HDRS =21.1	15/15 on AD	10.3 years	Excluded	Age, sex, handedness and education	3
Zhou et al. (2010) [119]	23 (10/13)	31.1 (10.4)	23 (10/13)	36.6 (12.9)	17-HDRS = >18	23/23 Medication-naïve	7.6 months	Excluded	-	3

AD = Antidepressants, TRD = Treatment-Resistant Depression, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery–Asberg Depression Rating Scale, GDS = Geriatric Depression Scale, SCAN = Schedules for Clinical Assessment in Neuropsychiatry, BDI = Beck Depression Inventory

The DLPFC has been consistently implicated in MDD, with reduced volume observed in the majority of studies [27–31], including in medication-naïve and medication-free MDD patients [32]. In a study of medication-naïve subjects, Wu et al. [33] reported abnormalities in white matter fibres compromising the connectivity within dorsolateral–prefrontal circuits. Healthy controls with a family history of MDD have also been shown to exhibit smaller volumes of white matter in the DLPFC [14]. As the DLPFC plays an important role in working memory and executive functions, disruptions of the DLPFC, in connection with other cortical and subcortical regions as part of the limbic–cortical dysregulation model, contribute to diminished cognitive ability and disturbances in social behaviour and emotional regulation [34].

Reductions in orbitofrontal cortex (OFC) volume in MDD are thought to be associated with functional alterations in the network of emotion regulation [35]. In a study that combined fMRI and VBM methods, unmedicated patients performing a Stroop task demonstrated hyperactivation of the ACC that was inversely correlated with GMV reduction in the OFC [27]. Frodl et al. [36] reported decreased connectivity between the OFC and the ACC, thought to be associated with a deficit in regulating self-schemas, and increased connectivity between the OFC and the DLPFC, demonstrating greater neural response to negative stimuli in drug-free patients with MDD. In resting-state fMRI, Zhang et al. [37] reported a decrease in functional activity in an affective network between the amygdala and OFC in first-episode medication-naïve MDD adolescents.

One of the most replicated findings in MDD is decreased hippocampal volume [38, 32], which is evident at the first episode of depression [39]. Recurrent episodes can lead to further volume reductions in the hippocampus over the course of the disorder, which may also contribute to symptoms of cognitive decline in MDD [40].

MDD is also associated with increased GMV in the thalamus [31, 32, 41] and the right insula [31] of medication-naïve first-episode MDD individuals. Decreased grey matter density in the thalamus has been proven to be a significant diagnostic marker of depression in medication-free MDD [42]. The thalamus has extensive connections with cortical and limbic structures and is believed to be involved in consciousness, awareness, and arousal. Abnormal functioning of the thalamus may contribute to symptoms such as disturbed sleep patterns. The insula is a structure that has been implicated in interoceptive awareness [43]. During an interoceptive attention task, the dorsal mid-insula exhibited decreased activity in unmedicated MDD subjects compared to controls [44]. Decreased activity has also been associated with severity of depression and somatic symptoms in depressed subjects.

Structural Changes with Antidepressant Treatment

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), which are widely used in the treatment of depression, have been reported

to alter the structure of frontal-subcortical circuits involved in the pathophysiology of depression [31, 45, 46•, 47, 48].

Increases in hippocampal volume have been reported following eight weeks of treatment with citalopram [46•] as well as following three years of treatment with various antidepressant medications [47]. Volume increases have also been reported in the dorsolateral and orbitofrontal cortices following treatment with fluoxetine [31]. The hippocampus is involved in declarative or explicit memory function [49, 50], and these findings may be consistent with the amelioration of memory impairments in depressed patients [51] following antidepressant treatment [52, 53].

However, not all studies have found alterations in brain volume of depressed patients following antidepressant treatment [54, 55]). In addition, a decrease in volume in the dorsolateral prefrontal cortex has been reported [56]. More research is needed to delineate volume change and direction of volume change associated with antidepressant treatment and improved mood and function.

Functional Changes with Antidepressant Treatment

The effects of antidepressant treatment on affective processing networks have been more widely studied, as there is a mood-congruent processing bias evident in patients with depression. This negative bias is evident in the processing of facial expressions [57], and MDD patients show both implicit and explicit attentional biases toward negative stimuli and away from positive stimuli [58]. fMRI studies often use implicit emotional processing paradigms such as a gender decision task, as these tasks are more likely to elicit activations in subcortical and extrastriate cortical regions [59].

Implicit processing of sad facial expressions has revealed abnormal activations in corticolimbic regions such as the amygdala [24, 60], insula and anterior cingulate [24] at baseline, followed by significant decreases in the amygdala following treatment with antidepressants [24, 62]. Happy facial expressions, on the other hand, tend to be associated with decreased corticolimbic activations in patients compared to controls, and which normalize following antidepressant treatment [63]. Moreover, amygdala activations are also observed during passive viewing of negative stimuli [16, 64] which attenuate with treatment [64]. Conversely, explicit labelling of emotions is likely to decrease the probability of amygdala activation compared to passive viewing or implicit processing [59]. There is also some evidence of a lateralization of amygdala activations in which the left rather than the right amygdala is more likely to be activated during processing of evident unmasked emotional stimuli [65–67], and therefore may be more functionally inclined to modulation by antidepressants [67].

The fusiform gyrus is important in face processing [65], and is typically engaged during explicit processing of emotional stimuli. Similar to amygdalar responses, fusiform gyrus activations are seen in patients versus controls during negative emotional processing, while decreased activations have been observed in patients during processing of positive emotional stimuli [68]. Normalization of the fusiform gyrus activity after antidepressant

treatment is seen during both positive [69] and negative [61] emotional stimuli, suggesting that antidepressants modulate regions that are associated with emotion dysregulation in depression.

In addition to biases in emotional processing, depression is associated with cognitive impairments leading to difficulties in memory and attention. The anterior cingulate is more likely to be activated during tasks of cognitive demand [24, 70], and fMRI studies of cognitive processing have shown increased rostral anterior cingulate activity during Stroop tasks [71, 72] and tasks of cognitive control [73]. Subregions of the anterior cingulate cortex – namely the pregenual and the subgenual ACC – are important targets for antidepressant action [74], and normalization of the frontocingulate activity has been observed with antidepressant treatment [73].

It has been proposed that depression results from abnormal connections between the limbic regions, such as the amygdala, and other parts of the brain. Therefore, in addition to investigating regional brain activations, studies have also looked at the interaction between brain regions that are impaired in depression. Patients with depression show reduced functional connectivity between the frontocortical and limbic regions [16, 19, 67], which is improved following treatment with antidepressants [67].

Activation in the anterior cingulate and orbitofrontal cortex during an acute depressive episode is predictive of subsequent clinical response [6••]. In addition, differences in functional orbitofrontal cortex connectivity prior to treatment have been shown to distinguish responders from non-responders [75]. The anterior cingulate and orbitofrontal cortices play an important role in emotional processing, and the orbitofrontal cortex is particularly associated with reward and hedonic experience [76]. Greater pre-treatment activity in these regions may suggest better ability to process emotions and greater responsivity to hedonic stimuli, and therefore predictive of a clinical response [6••].

Functional Changes with Cognitive Behavioural Therapy

Fewer studies have investigated the neural correlates of emotional processing following psychotherapy. Most studies have investigated cognitive behavioural therapy (CBT), an effective treatment for major depressive disorder, with rates of efficacy comparable to antidepressant medication [77], and which focuses on modifying dysfunctional thinking and behaviour that are common in depression [78].

Elevated baseline amygdala-hippocampal activity has been identified in depressed patients in comparison to healthy controls during implicit processing of sad facial expressions which ameliorates following a course of cognitive behaviour therapy [60]. Other reported changes in depressed patients following cognitive behavioural therapy have included decreased activation in the medial prefrontal cortex (mPFC) and ventral anterior cingulate cortex (vACC) in response to an emotional processing task [79] and during self-referential processing of negative words [80]. The medial prefrontal cortex is thought to play an important role in self-referential processing of negative stimuli [81], which is a central feature of rumination and depression [82]. These functional changes in activity following CBT treatment may reflect an increased engagement of processes involved in modulating responses to

affect-laden stimuli compatible with a "top-down" mechanism of action [83].

This cortical top-down model of cognitive therapy focuses on altering memory and attention processes that are involved in the mediation of cognitive biases and maladaptive processing of information [84]. There is evidence to suggest that antidepressants may have a mechanism of action similar to cognitive therapy in modulating negative biases and memory impairments in depression, occurring very early in the course of treatment, even before patients report any change in their mood or anxiety [85••, 86]. As such, these treatments may have similar neurobiological mechanisms on common underlying processes, leading to improvement in depression.

Clinical Neuroimaging Biomarkers in Depression

In addition to examining treatment effects in major depression, identifying biomarkers of clinical response may aid in treatment recommendations as well as in the development of novel strategies to augment existing treatment methods. Our meta-analysis of both pharmacological and psychological treatment studies revealed that higher pre-treatment anterior cingulate activity was a consistent predictor of clinical response, while reduced baseline hippocampal volume and increased insula and striatum activity were indicative of a poorer clinical response [6••]. Anterior cingulate activity as a predictor of clinical response has been widely reported across different antidepressant treatment studies using a variety of tasks, including resting-state [87, 88], emotion processing [23, 74, 89], and cognitive [90] tasks. The predictive function of the anterior cingulate is usually observed in response to negative rather than positive emotional stimuli [23, 74, 89]. Whilst there is strong evidence for increased baseline activation in the anterior cingulate as a predictor for antidepressant response, the evidence for CBT has been more mixed [6••], in part due to the limited number of studies. Further investigation is warranted.

To translate these findings into clinical application, it is important to identify clinical biomarkers with high predictive accuracy at the individual level [5•]. Using neuroimaging measures, it has been possible to identify biomarkers of clinical response even before the start of treatment. To date, there are no biological markers that are used to diagnose the disorder or to predict clinical response. Methods of analyses based on machine learning algorithms have been applied to neuroimaging measures such as structural and functional data to predict diagnosis, course of illness, and treatment prognosis [7]. The pattern of baseline neural activity during sad facial expression accurately classified 84 % of MDD patients and 89 % of healthy controls [4••], while neural correlates of verbal working memory showed reduced accuracy [90]. Baseline neural activity during sad facial processing predicted remission to CBT with a sensitivity of 71 % and specificity of 86 % [91], while remission to antidepressants showed a trend towards significance [4••]. Evidence from structural data, on the other hand, revealed that grey matter density predicted clinical response to antidepressant medication, in particular in the anterior cingulate [42, 92]. Further investigation of neuroimaging as well as other biological measures is required to develop clinically useful biomarkers. This would help optimize treatment strategies, especially for

those who may not benefit from current first-line treatment options that are available for depression.

Compliance with Ethics Guidelines

Conflict of Interest
Lauren Atkinson, Anjali Sankar, Tracey Adams, and Cynthia H.Y. Fu each declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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ORIGINAL ARTICLE

Neural effects of cognitive–behavioural therapy on dysfunctional attitudes in depression

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Background. Dysfunctional attitudes are a feature of depression that has been correlated with receptor binding abnormalities in limbic and cortical regions. We sought to investigate the functional neuroanatomy of dysfunctional attitudes in major depressive disorder (MDD) and the effects of treatment with cognitive–behavioural therapy (CBT).

Method. Participants were 16 patients with unipolar depression in an acute depressive episode (mean age 40.0 years) and 16 matched healthy controls (mean age 39.9 years). Patients were medication free and received a course of treatment with CBT. All participants underwent functional magnetic resonance imaging (fMRI) scans at baseline and at week 16, prior to the initiation of therapy and following the course of CBT for patients. During each fMRI scan, participants indicated their attributions to statements from a modified Dysfunctional Attitudes Scale (mDAS-48).

Results. MDD patients in an acute depressive episode endorsed a greater number of extreme responses to DAS statements, which normalized following CBT treatment. Extreme attributions were associated with greater activation in the left hippocampal region, inferior parietal lobe and precuneus in MDD patients as compared with healthy controls as a main effect of group. An interaction effect was found in the left parahippocampal region, which showed less attenuation in MDD patients at the follow-up scan relative to healthy controls.

Conclusions. Attenuation of activity in the parahippocampal region may be indicative of an improvement in dysfunctional thinking following CBT treatment in depression, while persistent engagement of regions involved in attentional processing and memory retrieval with extreme attributions reflects a trait feature of depression.

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Key words: Brain imaging, cognitive behavioural therapy, depression, dysfunctional attitudes, neuroimaging, psychotherapy.

Introduction

Beck (1967) postulated that early detrimental life events could lead to the development of negative schemas which include themes of loss, failure and abandonment. Dysfunctional attitudes, such as 'if I fail partly, it is as good as being a complete failure', are activated during stressful life events and are characteristic of a depressive episode (Haaga *et al.* 1991). It has been proposed that depressive symptoms are promoted by dysfunctional attitudes (Sheppard & Teasdale, 2000) in a reciprocal causal relationship (Burns & Spangler, 2001). In support, positive associations between depression severity and dysfunctional attitudes have been observed (Beevers *et al.* 2003), which revert to normal during remission (Haaga *et al.* 1991), and the magnitude of dysfunctional thinking during a dysphoric mood state is predictive of a subsequent depressive relapse (Segal *et al.* 2006).

High levels of dysfunctional thinking during a depressive episode have been associated with greater 5-HT_2 receptor binding potential in the anterior cingulate, prefrontal regions, thalamus, caudate and putamen (Meyer *et al.* 2004). Administration of the serotonin agonist D-fenfluramine led to a reduction in dysfunctional attitudes, suggesting that serotonin agonism can reduce dysfunctional attitudes by inducing neuronal release of serotonin in depression (Meyer *et al.* 2003). Although a correlation with receptor binding potential and attributions has been observed, subjects were not actively engaged in a dysfunctional attitudes task during the brain scan.

An aim of cognitive–behavioural therapy (CBT) is to address dysfunctional attitudes that contribute to the

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persistence of depressive symptoms (Dobson & Dozois, 2001). Following treatment with CBT, increased activity has been noted in the anterior cingulate during a resting state (Goldapple *et al.* 2004), in response to sad faces (Fu *et al.* 2008), and with self-referential processing to positive stimuli though not to negative stimuli (Yoshimura *et al.* 2014). Additional neural correlates of CBT in depression include normalization of amygdala activity to sad facial expressions (Fu *et al.* 2008), increases in ventromedial cortical activity (Ritchey *et al.* 2011), decreases in dorsal frontal cortical activity (Kennedy *et al.* 2007), and increases in hippocampal activity during a resting state (Goldapple *et al.* 2004). The changes in prefrontal, limbic and subcortical activity are generally consistent with models of neurocognitive circuits in depression and the effects of CBT (DeRubeis *et al.* 2008).

However, the brain regions engaged by dysfunctional thinking in depression and the effects of CBT have not been examined. In the present study, we sought to investigate the neural correlates of dysfunctional attitudes in patients with depression during an acute depressive episode and following treatment with CBT. We expected that patients would show greater endorsement of dysfunctional attitudes during an acute depressive episode, which we expected would improve following treatment with CBT. We hypothesized that major depressive disorder (MDD) patients would show greater activation in the anterior cingulate and regions associated with attention and self-referential processing with extreme attributions relative to healthy controls. We expected to observe increased activity in regions associated with attentional processing of negative stimuli in patients during an acute depressive episode which would resolve following CBT, including increased activity in the amygdala which would normalize following CBT.

Method

Participants

All participants were right handed and fluent in English. Participants were recruited through local newspaper advertisements. The study was approved by the Institute of Psychiatry and South London and Maudsley (SLaM) National Health Services (NHS) Ethics Research Committee, and all participants provided written, informed consent. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

The patient group consisted of 16 participants [13 women, mean age 40.00 years (S.D. = 9.27)] who met criteria for MDD by the Structured Clinical Interview for DSM-IV (First & Gibbon, 1997) and a clinical interview with a consultant psychiatrist. Inclusion criteria were an acute episode of MDD, unipolar subtype and a score of a minimum of 18 on the 17-item Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960). The exclusion criteria were a current neurological disorder, history of neurological trauma resulting in a loss of consciousness, history of diabetes or medical disorder, other Axis I disorders including anxiety disorder or history of substance abuse within 2 months of participation in the study. All patients were free of psychotropic medications for a minimum of 4 weeks at the time of recruitment (8 weeks for fluoxetine) and remained medication free throughout the treatment. HAMD score was measured at baseline and following the course of CBT at the end of 16 weeks.

Healthy controls were 16 age-, sex- and intelligence quotient (IQ)-matched healthy participants [13 women, mean age 39.94 years (S.D. = 9.48)] with HAMD scores less than 8 and no history of previous psychiatric illness, neurological disorder or head injury resulting in a loss of consciousness. All healthy controls were free of psychotropic medications. HAMD score was measured at baseline and at the end of 16 weeks.

Dysfunctional Attitude Scale (DAS)

The DAS measures pervasive negative attitudes towards the self, the world and the future. In the present study, the DAS-24 (Power *et al.* 1994) was used, which is a shortened version of the DAS (Weissman & Beck, 1978) consisting of 24 statements. Also, 24 neutral statements were included as a control task for the present study, which we have called the control DAS (cDAS). We have termed the 48-item scale as the 'modified Dysfunctional Attitude Scale' (mDAS-48).

During the functional magnetic resonance imaging (fMRI) scan, participants were presented with the mDAS-48 task consisting of statements alternating from the DAS and cDAS. Subjects were asked to respond to each statement using seven-point Likert scales, ranging from totally agree to totally disagree. Extreme responses are a reflection of the endorsement of dysfunctional attitudes (Power *et al.* 1994). The fMRI task began with either a DAS or cDAS statement which was presented in a counterbalanced order for consecutive participants, and the same version was used for the same participant. fMRI scans were acquired at baseline (week 0) and upon study completion (week 16). Each MRI scan was up to 1.5 h in duration consisting of fMRI tasks and structural MRI scans, and data from an affective facial processing task have been presented (Fu *et al.* 2008).

All behavioural data were recorded during the fMRI scans and analysed using SPSS (version: PASW Statistics 18). Repeated-measures analysis of variance (ANOVA) was used to analyse the main effect of group (patients *v.* controls), main effect of statement (DAS *v.* cDAS), main effect of time (week 0 *v.* week 16) and group × time interactions (i.e. changes in response between baseline and final trials). Percentage change in extreme attributions (total number of extreme DAS scores at week 16 − total number of extreme DAS scores at baseline/total number of extreme DAS scores at baseline × 100) was also calculated for each subject.

CBT treatment

Patients received 16 sessions of CBT with experienced therapists (Fu *et al.* 2008). The standard CBT procedures as described by Beck *et al.* (1979) were followed, and all therapists met the required level of training and proficiency (Paykel *et al.* 1999). The CBT sessions were audiotaped and reviewed to ensure adherence and competence. HAMD scores were obtained from patients at baseline and after 16 weeks of CBT. We defined treatment response as a minimum reduction of 50% in HAMD score from baseline.

Image acquisition

Gradient echo single-shot echoplanar imaging data were acquired on a neuro-optimized 1.5T IGE LX system (USA) at the Maudsley Hospital, London. A total of 441 T_2* weighted images depicting blood oxygenation level-dependent (BOLD) contrast were acquired over 27 min. For each volume, 22 near-axial non-contiguous 3 mm planes parallel to the intercommissural plane; time to echo (TE) = 40 ms; repetition time (TR) = 3.74 s; in-plane resolution = 3.75 mm; interslice gap 0.3 mm; and matrix size 64 × 64 voxels. Four dummy acquisitions were acquired at the beginning of each scan to allow magnetization to reach equilibrium amplitude.

fMRI data analysis

fMRI data analysis was conducted using XBAM software (version 4.1; Institute of Psychiatry, King's College London). Images were first realigned to minimize subject motion and then smoothed using a Gaussian filter (full-width half-maximum = 7.2 mm). Responses to the experimental paradigms were detected by carrying out time-series analysis using two gamma variate functions with peak responses at 4 and 8 s, respectively. The best fit between the weighted sum of these and the time series at each voxel was computed with a goodness of fit at each voxel. The ratio of the sum of squares (SSQ) of deviations from the mean image intensity due to the model over the whole time series to the SSQ of deviations due to the residuals was computed, termed the SSQ ratio. The data were then permuted by a wavelet-based method which permits the calculation of the null distribution of SSQ ratios under the assumption of no experimentally determined response. This distribution was used to calculate the SSQ ratio value and to find the threshold for the activation maps at type I error rate of less than one voxel. The SSQ ratio data for each individual were transformed into standard space of Talairach & Tournoux (1988).

Group activation maps were computed using the median SSQ ratio at each voxel in the observed and permuted maps. Permutation methods and median statistics were used to obtain the null distribution of SSQ ratios and as well as the critical SSQ ratio to threshold group activation maps at a cluster-level threshold of less than one expected type I error cluster per brain. For the present group analysis, less than one false-positive cluster was expected at $p < 0.05$ for voxel level and $p < 0.01$ at cluster level. Only those voxels at which all subjects contributed data were included for analysis (Fu *et al.* 2008).

In order to examine the neural correlates of dysfunctional attributions, the fMRI time series corresponding to attributions that corresponded to endorsements of 1, 2, 6 or 7 on the Likert scale were encoded. The fMRI time series associated with regular attributions were encoded by Likert scale responses of 3, 4 or 5. We employed a 2 × 2 ANOVA to examine the main effect of group (patients *v.* healthy controls across both time points), main effect of time (week 0 *v.* week 16) and the group × time interaction. The analyses were examined for regular attributions made to DAS relative to control DAS statements and for extreme attributions made to DAS relative to control DAS statements.

Results

Demographics

There were no significant group differences in mean age, full IQ, verbal IQ and performance IQ (all $p > 0.05$) (Table 1). All patients completed a full course of 16 weeks of CBT. There was an expected significant difference in HAMD scores between the groups at week 0 ($F_{1,30} = 1765.21$, $p < 0.001$) and at week 16 ($F_{1,30} = 18.96$, $p < 0.001$). Patients showed a significant reduction in mean HAMD scores from baseline to week 16 ($F_{1,15} = 118.45$, $p < 0.001$).

Behavioural data

The extreme responses to the DAS statements showed a significant group × time interaction effect

Table 1. *Demographic and clinical characteristics*

	Healthy controls	MDD patients
Participants, *n*	16	16
Sex, *n*		
Male	3	3
Female	13	13
Age, years	40.00 (9.27)	39.94 (9.48)
Full IQ	123.44 (10.63)	120.03 (14.02)
Verbal IQ	120.44 (11.98)	118.09 (15.95)
Performance IQ	122.31 (11.74)	118.34 (13.37)
Age of onset, years (range)	N.A.	33.8 (18–53)
Number of previous episodes (range)	N.A.	0.63 (0–2)
Duration of current episode, years (range)	N.A.	1.64 (0.2–4)
Number of treatment trials for present episode (range)	N.A.	0.13 (0–1)
HAMD scores at baseline	0.19 (0.05)	20.88 (1.89)
HAMD scores at week 16	0.56 (1.15)	6.37 (5.21)

Data are given as mean (standard deviation) unless otherwise specified.

MDD, Major depressive disorder; IQ, intelligence quotient; N.A., not applicable; HAMD, Hamilton Rating Scale for Depression.

Table 2. *Behavioural performance on the DAS task*

	Healthy controls	MDD patients
DAS task		
Week 0		
Extreme attributions	13.94 (4.11)	15.82 (5.45)
Regular attributions	10.06 (4.10)	8.18 (5.62)
Week 16		
Extreme attributions	14.44 (3.67)	12.94 (4.46)
Regular attributions	9.56 (3.67)	11.06 (4.46)
Control DAS task		
Week 0		
Extreme attributions	13.88 (4.44)	15.88 (3.84)
Regular attributions	10.12 (4.44)	8.12 (3.61)
Week 16		
Extreme attributions	14.12 (3.91)	13.43 (3.85)
Regular attributions	9.88 (3.91)	10.57 (3.85)

Data are given as mean (standard deviation).

DAS, Dysfunctional Attitudes Scale; MDD, major depressive disorder.

($F_{1,30} = 7.434$, $p = 0.011$), in which patients showed a significant reduction in mean number of extreme responses following a course of CBT [$t = 2.938$, degrees of freedom (df) = 15, $p = 0.010$] while healthy controls did not have a change in extreme scores at the follow-up scan as compared with baseline ($t = -0.659$, df = 15, $p = 0.520$) (Table 1). There was also a trend towards a significant effect of time ($F_{1,30} = 3.681$, $p = 0.065$), as both groups showed a reduction in extreme responses at the follow-up scan. There was no significant main effect of group in extreme responses ($F1,30 = 0.016$, $p = 0.900$) (Table 2).

In the control DAS statements, there were no significant main effects of time ($F_{1,30} = 2.054$, $p = 0.162$), group ($F_{1,30} = 0.140$, $p = 0.711$) or group × time interaction effects ($F_{1,30} = 3.343$, $p = 0.077$).

There were no significant correlations between the change in HAMD scores and the change in the number of extreme responses made to the DAS statements in MDD patients ($r = 0.465$, $p > 0.05$, one-tailed test). We were also interested in examining the relationship between changes in DAS scores and response to treatment. However, the number of patients who did not respond to treatment ($n = 3$) was insufficient to compare with those who responded. Hence, we report the mean percentage change in extreme DAS scores in responders (mean = −13.34, S.D. = 33.66) and non-responders (mean = −12.8, S.D. = 15.75).

fMRI results

Neural responses to extreme attributions in DAS

A significant group × time interaction effect for extreme attributions to DAS statements was found in the left parahippocampal gyrus [Brodmann area (BA) 37] (Talairach coordinates: x, y, z = −36, −41, −7, cluster size = 41 voxels, corrected $p = 0.0027$). This region showed less attenuation in activation in MDD patients as compared with healthy controls at the 16-week scan (Figs 1 and 2).

There was a significant main effect of group in which patients showed greater activation in the left

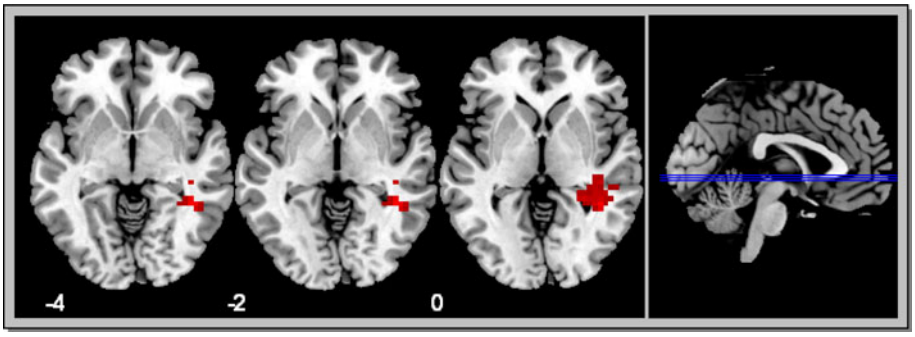

Fig. 1. There was a significant group × time interaction effect in the left parahippocampal region for extreme attributions to Dysfunctional Attitudes Scale statements (corrected $p = 0.0027$). Both depressed patients and healthy controls showed a decrease in activation in the left parahippocampal gyrus at the follow-up scans but to a lesser extent in patients. Transverse sections of the brain are presented with the Talairach z-coordinates indicated.

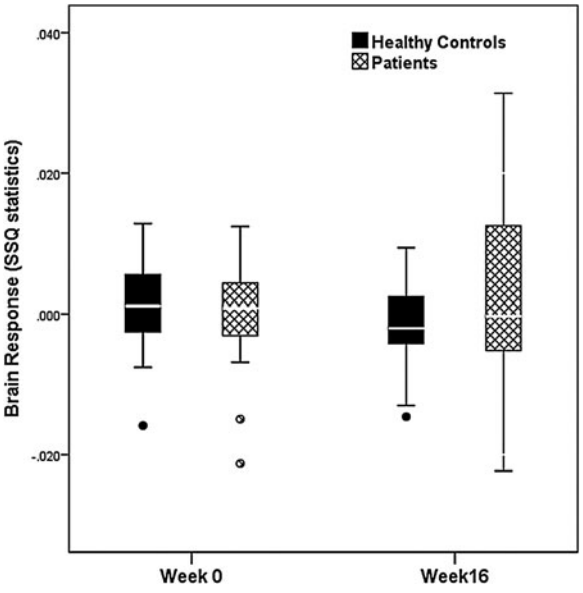

Fig. 2. The graph presents the group × time interaction effect in the left parahippocampal region. The boxes indicate interquartile range. The horizontal lines in the boxes represent medians. The limit lines indicate ranges excluding outliers, and the circles represent outliers which are defined as points greater than 1.5 times the interquartile range from the limits of the interquartile range. The *y*-axis sum of squares (SSQ) values represent a normalized statistic of the brain response.

hippocampal region (coordinates: x, y, z = −11, −33, −3, cluster size = 27 voxels, corrected $p = 0.0016$), left inferior parietal lobe (BA 40) (coordinates: x, y, z = −36, −33, 40, cluster size = 55 voxels, corrected $p = 0.0013$) and left precuneus (BA 7) (coordinates: x, y, z = −14, −67, 33, cluster size = 109 voxels, corrected $p = 0.00006$) as compared with healthy controls, while in the left cerebellum healthy controls showed greater activation relative to patients (coordinates: x, y, z = −11, −44, −23, cluster size = 45 voxels, corrected $p = 0.0016$) (Fig. 3).

In patients, a main effect of time was observed in the right posterior cingulate gyrus (BA 30) (coordinates x, y, z = 11, −44, 23, cluster size = 73 voxels, corrected $p = 0.006$) which showed decreased activation from week 0 to week 16, while no regions showed greater activation from the initial to the final scan. In healthy controls, no regions showed decreased activation from week 0 to week 16, but there was a significant main effect of time in the left cuneus (BA 18) (coordinates x, y, z = −18, −78, 17, cluster size = 53 voxels, corrected $p = 0.005$), which showed increased activation from the initial to the final scan.

Patients showed a significant positive relationship between changes in HAMD score and overall activity in the left precentral gyrus (BA 6) (coordinates x, y, z = −43, −4, 40; cluster size = 28 voxels, $r = 0.739$, corrected $p = 0.004$), in which patients with the greatest improvement in HAMD scores following CBT treatment had the greatest increase in activity in the precentral gyrus (Fig. 4).

Neural responses to regular attributions in DAS

There was no significant main effect of group or any group × time interaction effects in the neural responses to regular attributions to the DAS statements.

In patients, no regions showed decreased activation from the initial to final scan, but there was a main effect of time in the left cerebellum (Talairach coordinates x, y, z = −11, −74, −17, cluster size = 26 voxels, corrected $p = 0.0025$), which showed increased activation from weeks 0 to 16. In healthy controls, main effects of time were observed in the left lingual gyrus (BA 18), left parahippocampal gyrus and bilateral precuneus (BA 7) (corrected $p < 0.006$), which showed reduced activation from the initial to final scans and in the left inferior frontal gyrus (BA 10) (coordinates x, y, z = −36, 44, 3, cluster size = 36 voxels, corrected

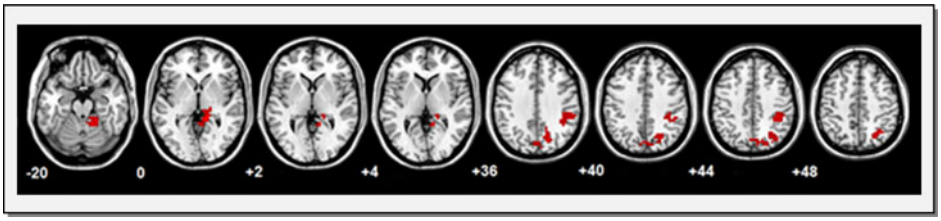

Fig. 3. In the main effect of group, major depressive disorder patients showed significantly greater activation in the left hippocampus (corrected $p = 0.0016$), left inferior parietal lobe (corrected $p = 0.0013$) and left precuneus (corrected $p = 0.0006$), relative to healthy controls. Healthy controls showed a greater activation in left cerebellum (corrected $p = 0.0016$) compared with depressed patients. Transverse sections of the brain are presented with the Talairach z-coordinates indicated.

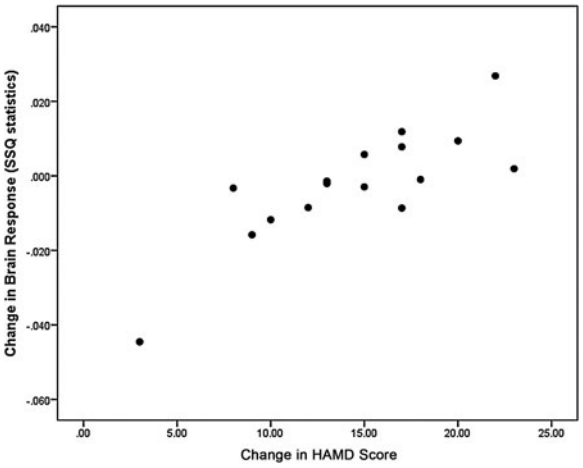

Fig. 4. A significant correlation was found between the change in the severity of depression as measured by the Hamilton Rating Scale for Depression (HAMD) scores and activity in the left precentral gyrus. Patients who had the greatest change in HAMD score following cognitive–behavioural therapy showed the greatest increase in activity in the left precentral gyrus during processing of dysfunctional attitudes. The *y*-axis sum of squares (SSQ) values represent a normalized statistic of the brain response.

$p = 0.003$) which showed increased activation from the initial to final scans.

Main effects of the DAS task and group are presented in the online Supplementary material.

Discussion

The present study supports a modifying effect of CBT on dysfunctional attitudes (Haaga *et al.* 1991; Furlong & Oei, 2002) as patients endorsed a greater number of extreme responses to DAS statements during an acute depressive episode which normalized following CBT. Dysfunctional attitudes are also seen to reduce following antidepressant treatment (Shankman *et al.* 2012), suggesting that they may be a state feature of depression. Parallel decreases in levels of dysfunctional attitudes and the severity of depression following CBT have also been noted (Persons & Burns, 1985), although dysfunctional attitudes have also been observed as a trait feature of depression (Roberts & Gamble, 2001). However, we did not observe a correlation between an improvement in depression severity and a reduction in extreme DAS attributions, as all patients showed an improvement in their extreme attributions.

The neural correlates revealed that endorsement of dysfunctional attitudes was associated with left parahippocampal activation in both depressed patients and healthy controls, which decreased at the follow-up scans in both groups but to a lesser extent in patients. The parahippocampal region along with the hippocampus and association areas of the cerebral cortex form the medial temporal lobe system (Eichenbaum & Lipton, 2008). There is a bidirectional hierarchy of reciprocal connections in which the cortical association areas connect to the parahippocampal region and in turn to the hippocampus. The output from the hippocampus is then returned to the parahippocampal region and to the cortical regions where the input originated (Eichenbaum & Lipton, 2008). The parahippocampal region is associated with contextual associations or episodic memory and shows a familiarity effect during repetition of tasks, with greater activation during novel as compared with familiar tasks (O'Kane *et al.* 2005).

Depressed individuals have shown greater activation in the left parahippocampal gyrus relative to controls, during encoding of an associative learning paradigm (Werner *et al.* 2009) and in processing negative pictures (Sheline *et al.* 2009). Reductions in parahippocampal activation have similarly been observed in MDD patient following treatment with antidepressant medication (Kennedy *et al.* 2001; Delaveau *et al.* 2011). Behavioural studies of dysfunctional attitudes also show higher endorsement of dysfunctional attitudes by patients relative to controls during negative mood induction (Lau *et al.* 2012) and significant improvement in dysfunctional thinking in patients following CBT (Warmerdam *et al.* 2010). To date, there

has been no fMRI study that has investigated the neural correlates of dysfunctional attitudes in depression, and therefore we cannot make direct comparisons to confirm the role of the parahippocampal gyrus in dysfunctional attitudes. However, left parahippocampal activation seems to be especially associated with negative stimuli (Iidaka *et al.* 2002; Surguladze *et al.* 2005), and activation in this region in both patients and in controls during presentation of DAS statements supports the role of the left parahippocampal gyrus in processing negative information contained in the DAS statements. The reduction in parahippocampal activation at the follow-up scan for both groups is consistent with increased familiarity with repetition of the task, although patients did not demonstrate the same extent in the reduction in activation. This may perhaps reflect patients' inability to recall the task in the same manner as controls in part due to persistent engagement and contextual associations to the DAS statements.

In the main effect of group across both time points, there was greater activation in a region that encompassed the left hippocampal gyrus, inferior parietal lobe and precuneus in patients relative to healthy controls. The inferior parietal lobe plays a prominent role in attention (Pessoa *et al.* 2002), processing of written language (Eckert, 2004), working memory of emotional stimuli (Rämä *et al.* 2001), and during episodic memory retrieval (Maddock *et al.* 2001). The increased activation observed in MDD patients relative to controls in the inferior parietal lobe may have reflected their greater attention in the processing of DAS statements along with the retrieval of associated memories. The precuneus is implicated in the visual processing of information including the retrieval of episodic memory which is modulated by attention (Cavanna & Trimble, 2006). In depression, the precuneus has been engaged by visual presentation of negative emotional stimuli (Phillips *et al.* 2004) and by sad relative to happy stimuli (Keedwell *et al.* 2005). The increased activity in the precuneus in MDD patients probably reflects increased attention during visual processing of DAS statements. The circular causality hypothesis (Burns & Spangler, 2001) proposes that dysfunctional attitudes and negative emotions have a reciprocal causal effect, which may have been induced by the DAS statements.

Furthermore, improvement in the severity of depressive symptoms showed a significant positive correlation with left precentral activity. The precentral gyrus plays an important role in successful response inhibition, while patients in an acute depressive episode tend to show impaired response inhibition (Schmid *et al.* 2011). Increased activity in the left precental gyrus has been reported in patients following treatment with psychotherapy (Dichter *et al.* 2009). Larisch *et al.* (1997) found significant positive correlations between dopamine (D_2) binding changes in the left precentral gyrus and an improvement in depression scores following antidepressant treatment, and the left precentral gyrus shows increased functional connectivity with the orbitofrontal cortex at baseline in subsequent responders to antidepressant treatment relative to non-responders (Lisiecka *et al.* 2011). The positive association between precentral activity and depression scores in the present study could reflect the improvements in inhibitory control in patients as they recovered from an acute depressive episode.

It was notable that the group differences in neural responses to extreme attributions to the DAS statements were not found with the regular attributions to DAS statements, reflecting the specificity of the neural effects to extreme attributions. However, contrary to our hypothesis, we did not find evidence for increased amygdala activity in MDD patients. The probability of amygdala activation is greater during passive processing of emotional stimuli rather than tasks involving any form of attentional effort, and language is associated with a significant reduction in amygdala activity (Costafreda *et al.* 2008). In the present study, DAS statements were presented as sentences and participants were required to make an active judgement in response, which probably contributed to the low elicitation of amygdala responsivity with the DAS statements. Furthermore, the present study was limited by the lack of a patient group who received a placebo treatment. We are unable to conclude with certainty that the significant difference in brain activation in patients is as a result of treatment with CBT. Future research should also investigate whether a reduction in dysfunctional thinking is evident with antidepressant treatment.

In summary, the present study supports findings that dysfunctional thinking is characteristic of major depression. Extreme attributions to DAS statements are indicative of dysfunctional thinking, and MDD patients showed a significant decrease in extreme attributions following CBT. MDD patients demonstrated persistently greater activity in regions associated with attentional processing and memory retrieval that was induced by the DAS statements. Attenuation of parahippocampal activity was observed at the follow-up scans in both groups, though to a lesser extent in the MDD patients, perhaps reflecting an improvement in dysfunctional thinking with some persistent vulnerability.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291714002529.

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Declaration of Interest

C.H.Y.F. has received research grant support from GlaxoSmithKline and Eli Lilly. J.S. has received expenses to attend conferences; she or her supporting institution has received fees for lecturing from AstraZeneca, Janssen-Cilag, Lundbeck and Servier; and her supporting institution has received an unrestricted grant from AstraZeneca. A.S., A.P., V.P.G. and H.S. report no competing interests.

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RESEARCH ARTICLE Open Access

Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine

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Abstract

Background: Longitudinal neuroimaging studies of major depressive disorder (MDD) have most commonly assessed the effects of antidepressants from the serotonin reuptake inhibitor class and usually reporting a single measure. Multimodal neuroimaging assessments were acquired from MDD patients during an acute depressive episode with serial measures during a 12-week treatment with the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine.

Methods: Participants were medication-free MDD patients (n = 32; mean age 40.2 years) in an acute depressive episode and healthy controls matched for age, gender, and IQ (n = 25; mean age 38.8 years). MDD patients received treatment with duloxetine 60 mg daily for 12 weeks with an optional dose increase to 120 mg daily after 8 weeks. All participants had serial imaging at weeks 0, 1, 8, and 12 on a 3 Tesla magnetic resonance imaging (MRI) scanner. Neuroimaging tasks included emotional facial processing, negative attentional bias (emotional Stroop), resting state functional MRI and structural MRI.

Results: A significant group by time interaction was identified in the anterior default mode network in which MDD patients showed increased connectivity with treatment, while there were no significant changes in healthy participants. In the emotional Stroop task, increased posterior cingulate activation in MDD patients normalized following treatment. No significant group by time effects were observed for happy or sad facial processing, including in amygdala responsiveness, or in regional cerebral volumes. Reduced baseline resting state connectivity within the orbitofrontal component of the default mode network was predictive of clinical response. An early increase in hippocampal volume was predictive of clinical response.

Conclusions: Baseline resting state functional connectivity was predictive of subsequent clinical response. Complementary effects of treatment were observed from the functional neuroimaging correlates of affective facial expressions, negative attentional bias, and resting state. No significant effects were observed in affective facial processing, while the interaction effect in negative attentional bias and individual group effects in resting state connectivity could be related to the SNRI class of antidepressant medication. The specificity of the observed effects to SNRI pharmacological treatments requires further investigation.

Trial registration: Registered at clinicaltrials.gov (NCT01051466).

Keywords: Antidepressant, BOLD, Brain, Function, Prognosis, Predictor, Structure

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Background

Major depressive disorder (MDD) is characterized by a prolonged low mood, neurovegetative disturbances, and cognitive impairments. Neuroimaging has aided in the delineation of the neural circuitry of MDD [1,2], determination of the effects associated with a course of therapy [3-5], provision of novel insights for neuropsychological models [2], and the potential for the development of prognostic and diagnostic biomarkers [6,7].

Within the neural circuitry of MDD, the intensity of engagement and their regional distribution depend in part on the emotional and cognitive features of the particular task. For example, in response to negative stimuli, MDD patients tend to show greater responsivity in the amygdala, dorsal anterior cingulate and insula, but reduced activity in the dorsolateral prefrontal cortex and striatum relative to healthy participants, while measures of resting state have most commonly revealed greater regional cerebral blood flow in the thalamus [5]. Studies have generally reported findings from a single task, while concurrently acquired, multiple functional and structural measures may provide a more comprehensive assessment [1-6,8]. Furthermore, longitudinal treatment studies have most frequently investigated the serotonin reuptake inhibitors (SRI), in which reduced activity in subcortical and limbic regions in MDD patients has been noted following treatment [3-5]. However, the effects of the SRI class of antidepressants may not necessarily be extrapolated to norepinephrine reuptake inhibitors (NRI) [9-12].

The present study is a multimodal investigation of the functional and structural neuroanatomy of depression in a prospective, longitudinal design with the dual serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine. MDD patients participated in MRI scans during an acute depressive episode and during the course of treatment, and healthy controls had the same scans at the same time points. Our main hypothesis was that treatment would be associated with normalization of anterior cingulate and amygdala activation in response to sad faces in MDD patients as compared with healthy participants [3-5].

Methods

The study was approved by the Cambridgeshire 4 Research Ethics Committee, NHS Research Ethics Committee, National Research Ethics Service, NHS Health Research Authority, and all participants provided informed written consent. The study was conducted in conformity with the Declaration of Helsinki and its amendments. Study procedures and implementation were consistent with Good Clinical Practice Guidelines and all applicable regulatory requirements.

Participants

Participants were recruited from the general community by newspaper advertisement. Inclusion criteria for all participants were an age range of 25 to 65 years and being right-handed. MDD patients met criteria for a single episode of MDD or recurrent MDD, without psychotic features, as defined by the *Diagnostic Statistical Manual of Mental Disorders*, Fourth edition, text revision (DSM-IV-TR) [13] and assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV) [14]; were free of current antidepressant medication for a minimum of 6 weeks for fluoxetine treatment or 4 weeks for other antidepressant medication before the start of treatment at baseline (week 0); and had a 17-item Hamilton Rating Scale for Depression (HRSD-17) [15,16] total score ≥ 18 at the screening assessment and baseline. Healthy participants were matched by age, gender, and intelligence quotient (IQ); had HRSD-17 total score ≤ 7 at screening and baseline; and did not meet criteria for MDD based on SCID-IV. IQ was evaluated with the Wechsler Adult Intelligence Scale-III UK (WAIS-III UK) [17].

Exclusion criteria were any significant comorbid medical or psychiatric disorders, as defined by DSM-IV-TR Axis I or II disorder including a history of substance abuse or dependence within the prior 6 months, excluding nicotine and caffeine; known Alzheimer's disease or mental retardation; serious suicidal risk or risk of self-harm (Columbia-Suicide Severity Rating Scale) [18]; history of electroconvulsive therapy, transcranial magnetic stimulation, or vagus nerve stimulation within the past year; abnormal thyroid stimulating hormone concentration; or medical disorders known to affect central nervous system structures or function.

Enrolled in the study were 32 MDD patients, having a moderate to severe severity of depression (mean HRSD-17 = 22.4 (standard deviation (SD) = 2.7)), and 28 healthy participants, with no significant between-group differences in demographics (Table 1). Twenty-four MDD patients and 23 healthy participants completed all the serial MRI scans.

Study design

The protocol consisted of a 12-week treatment period for MDD patients with duloxetine at a dosage of 60 mg once daily for the first 8 weeks. At week 8, MDD patients whose symptoms met criteria for remission continued taking 60 mg once daily, while those who did not had an optional dosage-increase up to 120 mg once daily (Additional file 1: Figure S1).

At baseline, MDD severity was evaluated with the following scales: SCID-IV [13], HRSD-17 [14,15], Hamilton Anxiety Rating Scale (HAMA) [19], Columbia-Suicide Severity Rating Scale (C-SSRS) [18], Clinical Global

Table 1 Demographics and baseline characteristics

	MDD patients	Healthy participants
Number	32	25[a]
Age	40.2 (11.2)	38.8 (9.9)
Age range	25.0-57.9	27.3-58.2
Male	19 (59.4 %)	12 (48.0 %)
Ethnicity		
White	18 (56.3 %)	15 (60.0 %)
Asian	10 (31.3 %)	3 (12.0 %)
African descent	4 (12.5 %)	7 (28.0 %)
Current alcohol use	22 (68.8 %)	19 (76.0 %)
Current tobacco use	6 (18.8 %)	1 (4.0 %)
HRSD-17	22.4 (2.7)	0.5 (1.3)
HAMA	21.1 (5.8)	0.4 (0.9)
WAIS-III	107.4 (11.2)	109.2 (14.6)
CGI-S	4.4 (0.6)	1.0 (0.0)
PGI-S	3.8 (1.1)	NA
SDS	19.3 (5.4)	0.2 (0.8)

All values are presented as mean and standard deviation in parenthesis, except where indicated. Age is in years. Number of participants and percentage of participants are presented for Male gender, Ethnicity, Current alcohol and tobacco use. Total scores are presented for HRSD-17, HAMA, WAIS-III and SDS. Participants were matched by age ($p = 0.62$), gender ($p = 0.39$), and WAIS-III IQ ($p = 0.61$) with no significant difference between groups, similarly for alcohol ($p = 0.55$) and drug use ($p = 0.12$). Abbreviations: CGI-S, Clinician Global Impression of Severity scale; HAMA, Hamilton Anxiety Rating Scale; HRSD-17, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; NA, not applicable; PGI-S, Patient Global Impression of Severity scale; SDS, Sheehan Disability Scale; WAIS-III, Wechsler Adult Intelligence Scale third UK edition. [a]excluding 3 inadvertently enrolled healthy participants who did not meet entry criteria.

Impression of Severity scale (CGI-S) [20], Patient Global Impression of Severity scale (PGI-S) [20], and Sheehan Disability Scale (SDS) [21]. IQ was evaluated with the WAIS-III UK [17] at weeks 0, 1, or 4. At each subsequent visit, the following assessments were performed: clinical assessment and administration of HRSD-17, HAMA, CGI-S, SDS, and PGI-S by a consultant psychiatrist or senior resident in psychiatry under supervision by a consultant psychiatrist. Response to treatment was defined as a minimum of 50% reduction from the week 0 (baseline) HRSD-17 total score. Remission was defined as an endpoint HRSD-17 total score of ≤ 7. During the study, safety and tolerability to treatment was assessed through collection and monitoring of discontinuation rates, treatment-emergent adverse events, serious adverse events, vital signs, laboratory analyses, and clinical assessments including questioning of suicide-related behavior and ideations using the C-SSRS.

Healthy participants were evaluated at baseline with the following rating scales: SCID-IV, HAMA, and WAIS-III UK. All visits were reviewed with a consultant psychiatrist.

Functional and structural MRI data acquisition

Magnetic resonance imaging (MRI) scans were acquired on a 3 Tesla GE SIGNA HDx (Milwaukee, WI, USA) at King's College London. MRI scans were acquired at weeks 0, 1, 8, and 12 for all participants.

Structural MRI scan

A high-resolution 3-dimensional sagittal T1-weighted structural image was acquired at each session (Magnetization Prepared Rapid Gradient Echo; resolution 1 mm^3). The functional MRI tasks included affective facial expressions [4,22,23], negative attentional bias task (emotional Stroop) [24], and resting state [8].

Affective facial expressions functional MRI task

The event-related functional MRI paradigm consisted of facial expressions and baseline trials presented in a random order [4,22,23]. Each facial stimulus was presented twice at each intensity (60 faces in total), along with 12 baseline trials consisting of a crosshair for a total of 72 presentations. Facial stimuli consisted of 10 faces (5 females) adapted from Pictures of Facial Affect by Ekman and Friesen morphed to represent varying intensities: low, medium and high [25]. Each stimulus was presented for 3 seconds. The interval between trials varied randomly according to a Poisson distribution, with a mean intertrial interval of 5 seconds, for a total duration of 360 seconds (6 minutes). Participants were instructed to specify the gender of the face (male, female), and responses were made by pressing a button.

Gradient echo T2*-weighted echoplanar images were acquired depicting blood oxygenation level-dependent (BOLD) contrast. A total of 180 volumes were acquired for each for the happy and sad facial tasks. For each volume, 39 oblique axial slices parallel to the intercommissural plane were collected with the following parameters: slice thickness: 3 mm, slice gap: 0 3 mm, echo time (TE): 30 milliseconds, repetition time (TR): 2000 milliseconds, flip angle: 75°, field of view: 240 mm, and matrix size: 64 × 64.

Emotional Stroop functional MRI task

The emotional Stroop task consisted of 40 negative and 40 neutral words presented in alternating blocks of eight words per emotional and neutral category, repeated five times. Each word was presented only once with a presentation time of 700 milliseconds per word. All words appeared on a dark grey background in red, blue, green, or yellow color, pseudo-randomized across the two valence categories. Four different stimulus sets which varied in the order of presentation of emotional and neutral word category blocks were randomized between scan sessions. The task was projected onto a screen and viewed from a mirror inside the scanner.

Participants were instructed to name the color of the word as quickly as possible. A microphone was used to record vocal responses and to provide auditory feedback of vocal input. Reaction times to the onset of the vocal responses were measured. Verbal responses during the MRI scan were made in the absence of scanner noise as a clustered fMRI image acquisition sequence was used [24].

The emotional Stroop task was acquired in 133 T2*-weighted echoplanar images, for each volume: 39 oblique axial slices parallel to the intercommissural plane collected over 2000 milliseconds, allowing for a silent period of 2000 milliseconds in a clustered fMRI acquisition. TE: 30 milliseconds, flip angle: 90°, slice thickness: 3 mm, interslice gap: 0.3 mm, matrix size: 64 × 64. The first 4 volumes collected were acquisitions to allow for T1 equilibrium effects.

Resting state functional MRI

Whole-brain functional resting state data were collected while participants were instructed to stay awake with their eyes closed and not to think of anything specific. Scan duration was 8.5 minutes. T2*-weighted single-shot gradient echo echoplanar sequence was acquired with the following parameters: TE: 30 milliseconds, TR: 2 seconds, FA: 75°, voxel size, 3.75 × 3.75 × 3.3 mm. Headphones and cushions were used to minimize scanner noise and head motion, respectively.

Pre-specified primary outcome measure and secondary analyses

The pre-specified primary outcome measure was the mean percentage signal change in functional MRI BOLD contrast response from baseline to week 12 in the mean of the right and left amygdalae, in response to sad facial affect processing, comparing MDD and healthy participants. The sample size for the study was based on effect size estimates for this primary outcome, obtained from our previous work on pre- to post- SRI treatment effects on amygdala activation in MDD patients relative to healthy controls [4].

Secondary outcomes included baseline-to-endpoint changes in illness severity, as assessed by HRSD-17, HAMA, CGI-S, Patient Global Impression of Improvement scale, and SDS global functioning impairment score, and their correlation with changes in structural and functional correlates over sessions in the following regions of interest: anterior cingulate cortices, amygdalae, and hippocampi. Changes in functional MRI BOLD contrast response and volumes of each region of interest from week 0 to weeks 1, 8, and 12 were analyzed using a restricted maximum likelihood-based mixed-effects model repeated measures (MMRM) approach. The model included the categorical effects of group, visit, and group-by-visit interaction as well as the continuous covariate of baseline measurement. Significance tests were based on least-square mean changes and Type III sum-of-square, implemented using SAS PROC MIXED (SAS, version 9 1, Cary, NC, USA). Logistic regression was also used to examine the association between endpoint remission and changes in neural correlates. The region-of-interest analyses were performed in all enrolled participants, using MMRM model or last observation carried forward (LOCF) methodology for missing observations (eg. participants who did not complete the study). No multiple comparisons correction procedures were applied to the MMRM analyses as these were pre-specified.

As well, functional whole-brain image analyses were conducted on a complete case basis involving each scan session (ie. with participants who participated in all four MRI scans) as standard software for whole-brain neuroimaging analysis does not permit "missingness" in the data set of images. As explained in detail below, whole-brain image analyses were focused on functional changes over time in the treatment and control samples, as well as prediction of treatment improvement (with HRSD-17 or HAMA) from baseline functional measurements. Complete data available for each task were varied due to scan acquisition difficulties, such as excessive movement during the scan and late arrival of participants leading to incomplete scan sessions. The number of participants who completed these tasks for all the scan sessions: happy and sad faces (23 MDD and 23 healthy participants); emotional Stroop (21 MDD and 20 healthy participants); and resting state (21 MDD and 20 healthy participants). Behavioral data are presented in the Additional file 1.

Functional and structural MRI analysis

Structural MRI analysis

Analysis of the structural images was performed with Freesurfer 4.5.0 automated longitudinal stream to obtain the volumes of *a priori* regions of interest: anterior cingulate cortices, amygdalae, and hippocampi [26]. Quality control was performed by visually assessing each Freesurfer brain segmentation overlaid on the original T1 image to ensure that cortical reconstructions did not present major anomalies. The medial temporal lobe region was assessed with coronal sections. All reconstructions passed this qualitative control, and the original Freesurfer outputs were used without manual corrections. High intraclass correlations (ICC) for repeated measurements were observed for all the volumetric measurements in the healthy control participants (all > 0.91) (Additional file 1: Table S1). Volumetric measurements of the amygdalae, hippocampi and anterior cingulate were included in second-level MMRM and logistic regression models.

Functional MRI analysis: task-related data

Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) was used to preprocess and analyze the task-related fMRI data. Images were realigned to correct for motion artifacts, spatially normalized to the Montreal Neurological Institute template, and smoothed using an 8-mm full-width at half maximum Gaussian kernel filter. Group analysis used a random effects model consisting of a 2-stage hierarchical procedure with the first-level analysis performed by using the general linear model, accounting for serial autocorrelations by application of an autoregressive model.

Affective facial expressions task

In the sad and happy faces tasks, stimuli presentations were modeled as individual events, and the first-level analysis produced contrast images relevant to the main contrast of interest (sad faces or happy faces vs. crosshair baseline). For the primary outcome measure, the MarsBar SPM toolbox was used to estimate mean activation in the *a priori* regions of interest.

Emotional Stroop task

In the emotional Stroop task, the first-level analysis produced individual mean images corresponding to the main contrast of interest (negative > neutral) and the time series was modeled as a block-design.

Second-level analysis of task-related functional tasks

For each task, its second-level analysis employed a random-effects model to examine the main effect of group (MDD vs. healthy participants across all time points), main effect of time (linear changes over weeks 0, 1, 8, and 12) and the group by time interaction. T-tests were also used to compare scanning data at a particular time point between groups. Inference of whole-brain statistical images was conducted using the general linear model and cluster-wise family-wise error rate control with $p < 0.05$ corrected for multiple comparisons. For *post hoc* analyses only, in order to identify the direction of changes responsible for an interaction effect, less conservative thresholds were also employed as indicated in the Results section.

Functional MRI analysis: resting-state data

Resting-state analysis was performed using FMRIB Software Library (FSL) v5.0 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Preprocessing included motion correction, skull stripping, spatial smoothing at 5 mm full-width at half maximum, and registration to standard space. Extraction of resting-state networks at the group level was conducted by using FSL Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) [27]. MELODIC was set to estimate 25 components to extract stable connectivity estimates of the default mode networks (DMNs) [8]. Five independent components depicting DMN activity were identified (Additional file 1: Figure S2) [28], encompassing the canonical default mode inclusive of the two core regions (anterior medial prefrontal and posterior cingulate cortices), dorsomedial prefrontal subsystem (dorsomedial prefrontal cortex, lateral temporal cortex, and temporoparietal junction), and medial temporal lobe subsystem (ventromedial prefrontal cortex including ventral cingulate, parietal lobule, retrosplenial cortex, and hippocampal formation) [29,30]. Dual regression was used to generate participant-specific and scan session–specific versions of group-level DMN spatial maps in two stages, resulting in a set of participant-specific spatial maps for each scan session and participant. *Second-level analysis of resting-state data:* Scan-specific maps were used to estimate contrast maps depicting linear changes across successive scans for each participant. These statistical maps (one per participant) were entered in a higher-level general linear model analysis, and statistical inference was performed with nonparametric permutation testing [31]. Correction for multiple comparisons was conducted using threshold-free cluster enhancement with family-wise error (FWE) rate control with $p < 0.05$ corrected for multiple comparisons [32].

Results

Clinical measures

MDD patients showed a significant improvement in their depression, as assessed by changes in HRSD-17 (−13.9 [7.0]); HAMA (−11.5 [8.6]); SDS global functioning impairment score (−9.8 [8.9]); and CGI-S (−2.2 [1.3]). Upon study completion at week 12, 18 MDD patients (75.0% of MDD completers) fulfilled criteria for remission and 19 MDD patients (79.1%) fulfilled criteria for clinical response. Applying the last observation carried forward analysis with inclusion of all enrolled participants, there were no significant differences in the history of depression between responders (n = 20, median 1 episode, mean 2.7 [4.43]) and non-responders which included MDD participants who did not complete the study (n = 7, median 2 episodes, mean 6.14 [10.53]) (p = 0.43). The frequency and nature of adverse events were consistent with the known profile of duloxetine [33], and there was one serious adverse event of retinal pigment epitheliopathy which was not judged to be related to the study or duloxetine.

Structural magnetic resonance imaging

There were no significant group by time effects nor any baseline differences in anterior cingulate cortices, amygdalae, or hippocampi volumes (Additional file 1: Table S1).

Affective facial expressions

Contrary to our hypothesis, there were no significant between group differences in the change in BOLD response from baseline to sad faces as analyzed with the MMRM approach nor any significant group by time effects from the whole-brain analysis. There were no significant differences between groups at baseline (Additional file 1: Table S1).

Within the MDD group, a main effect of time was observed in which there was a significant increase in the BOLD response to the mean of the medium and high intensity of expressions in the posterior cingulate/precuneus (x = −3, y = −43, z = 19; 221 voxels; peak T = 4.50; p (FWE corrected) = 0.010), while healthy participants showed a trend towards a decrease in the orbitofrontal region (x = 45,y = 29, z = 11; 118 voxels, T = 4.61, p (FWE corrected) = 0.068).

Similarly, no significant group by time effects or any baseline differences between groups were observed in the happy faces task. There were no main effects of time in the MDD patients, but healthy participants showed a significant decrease with time in response to the mean of medium and high intensity of expressions in the anterior cingulate (x = 9, y = 29, z = 40; 315 voxels, peak T = 4.27; p (FWE corrected) = 0.002) and precentral region (x = −51, y = 11, z = 34; 190 voxels; T = 4.08; p (FWE corrected) = 0.018), as well as approaching significance in the thalamus (x = 3, y = −13, z = 10; 118 voxels; T = 4.12; p (FWE corrected) = 0.070).

Emotional Stroop

A significant group by time interaction was observed in the left posterior temporoparietal junction involving the parahippocampal cortex (x = −18, y = −40, z = 1; 414 -voxels; peak T = 4.11; p (FWE corrected) = 0.014) as well as precuneus and posterior cingulate cortex (subordinate peaks at x = −24, y = −52, z = 22 and x = −21, y = −70, z = −10) during the processing of negative relative to neutral words (Figure 1). The interaction effect was found to be driven by reductions observed in MDD patients (significant at p = 0.001 uncorrected) with successive scans relative to healthy participants who showed no significant changes with time. At baseline, there was a main effect of group in which MDD patients showed greater activation relative to healthy participants in a region including the posterior cingulate cortex and precuneus bilaterally (right: x = 9, y = −43, z = 19; left: x = −15,y = −43, z = 4, and x = 15, y = −49, z = 13; -134 voxels; peak T = 4.51; p (FWE corrected) = 0.026).

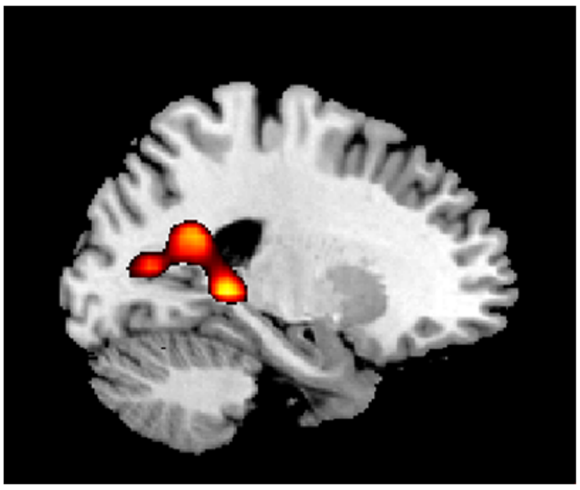

Figure 1 Emotional Stroop. A significant group by time effect was found for the emotional Stroop in the posterior cingulate extending into the precuneus.

Resting state

No significant group by time effects were found, but main effects of time were observed within each group. MDD patients showed decreased connectivity with successive scans (Figure 2) between DMN components and bilateral prefrontal cortices, namely with right dorsolateral (IC06; x = 52, y = 10, z = 18; 118 voxels; T = 3.9; 117 voxels; p (FWE corrected) = 0.034), right superior frontal premotor cortex (IC06; x = 22, y = −2, z = 64; T = 4.25; 41 voxels; p (FWE corrected) = 0.030), and left inferior frontal gyrus (IC06; x = −54, y = 14, z = 16; T = 4.79; 36 voxels; p (FWE corrected) = 0.018), as well as decreased connectivity between DMN components and auditory processing cortex (IC10; x = −57, y = −48, z = 19; T = 5.85; 1078 voxels; p (FWE corrected) = 0.007), and primary visual and extrastriate regions (IC20; x = 2, y = −78, z = 4; T = 4.88; 492 voxels; p (FWE corrected) = 0.005). Increases in connectivity between components of the DMN in MDD patients were found with medial prefrontal regions, including pregenual and subgenual cingulate and the frontal pole (IC08; x = 10, y = 30, z = −8; T = 5.04; 7287 voxels; p (FWE corrected) = 0.007), right hippocampus (IC24; x = 42, y = 14, z = −36; T = 4.13; 30 voxels; p (FWE corrected) = 0.023), parahippocampal gyrus (IC24; x = 42, y = −30, z = −20; T = 4.05; 431 voxels; p (FWE corrected) = 0.035), angular gyrus (IC08; x = 54, y = −46, z = 24; T = 4.99; 190 voxels; p (FWE corrected) = 0.010), and middle occipital gyrus (IC08; x = 10, y = −102, z = 8; T = 5.69; 263 voxels; p (FWE corrected) = 0.009). Healthy participants showed decreased connectivity with time between the DMN with the posterior hippocampus extending into the fusiform region (IC06; x = 30, y = −38, z = 0; T = 4.83; 45 voxels; p (FWE corrected) = 0.027). There was also increased connectivity with time in healthy participants between the DMN and posterior cingulate (IC08; x = 6, y = −50, z = 8; T = 3 78; 85 voxels; p (FWE corrected) = 0.030), fusiform gyrus (IC08; x = 34; y = −38, z = −12; T = 4.61; 375 voxels; p (FWE corrected) = 0.010), superior medial frontal gyrus (IC08; x = 2; y = 34, z = 36;

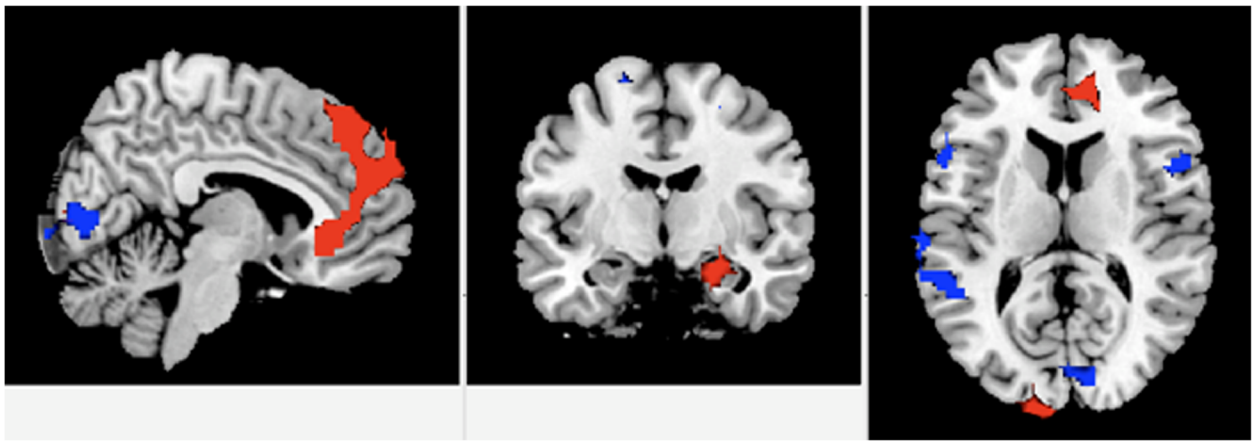

Figure 2 Resting-state functional magnetic resonance imaging. Linear changes in resting-state functional fMRI with successive scans, Areas with reductions in connectivity to the default mode network (DMN) regions with time are shown in blue, and areas with increased connectivity to the DMNs are depicted in red.

T = 3.85; 91 voxels; p (FWE corrected)- = 0.029), premotor cortex (IC08; x = −26; y = 10, z = 52; T = 4.19; 91 voxels; p (FWE corrected) = 0.025), and parietal lobule (IC08; x = 50; y = −54, z = 44; T = 4.30; 808 voxels; p (FWE corrected) = 0.006).

Predictors of clinical response

Baseline resting-state activity within the orbitofrontal component of the DMN in MDD patients, before treatment was initiated, was negatively correlated with improvement with treatment as measured by HRSD (Figures 3 and 4). MDD patients with reduced connectivity in the orbitofrontal component of the DMN (BA10/25/47) (left subgenual anterior cingulate (BA 25/11): x = 6, y = 30, z = −10; T = 6.84, 691 voxels; p (FWE corrected)- = 0.003; right subgenual/pregenual anterior cingulate: x = 12, y = 42, z = 8; T = 5.56; 83 voxels; p (FWE corrected)- = 0.021) showed the greatest improvement with treatment. No other functional MRI or structural baseline measures were correlated with changes in HRSD or HAMA based on the whole-brain analysis.

From the MMRM model, which accounted for participants who had not completed all the scans with a last observation carried forward methodology, an early increase in left hippocampal volume after 1 week of treatment predicted clinical remission following 12 weeks of treatment (odds ratio 1.01 (95% CI: 1.00, 1.02) p = 0.031) (Additional file 1: Table S2- S3). High intraclass correlations for repeated measurements were observed for all the volumetric measurements in the healthy control participants (all > 0.91), which were 0.976 and 0.961 for the right and left hippocampi, respectively (Additional file 1: Table S1).

Discussion

Distinct neural effects of treatment with duloxetine were revealed in resting state connectivity, affective facial processing, and negative attentional processing. Contrary to our hypothesis, we did not find any group by time

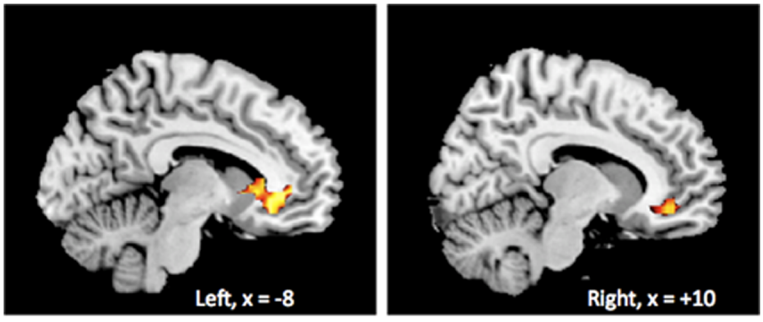

Figure 3 Baseline connectivity in ventral cingulate and orbitofrontal resting state network. Decreased baseline connectivity in ventral cingulate and orbitofrontal resting-state network predicted an improved response in correlation with the normalized change in HRSD-17 score from week 0 to week 12 corrected for multiple comparisons.

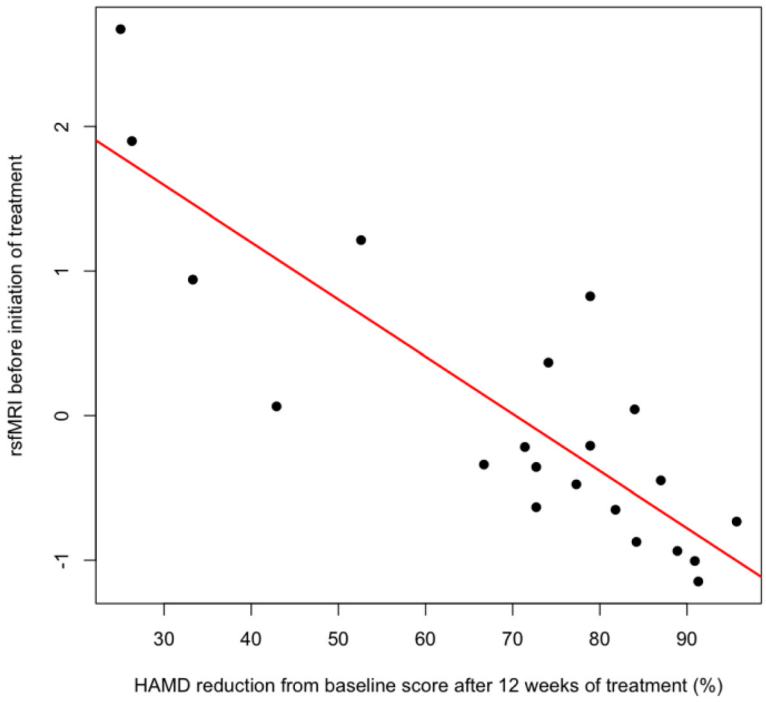

Figure 4 Association between baseline connectivity and change in depressive severity. Scatter plot of baseline resting-state fMRI baseline connectivity activity in subgenual cingulate and clinical response to 12 weeks of treatment with duloxetine as measured by the normalized change in HRSD-17 score from week 0 to week 12.

interaction effects in the neural responses to sad facial expressions [3-5]. Instead, marked effects in the posterior cingulate cortex were evident in response to a task designed to engage the negative attentional bias in MDD [24], and there were time-dependent changes in the DMN in MDD patients in which increased connectivity towards limbic regions but decreased connectivity with lateral cortical regions emerged as treatment progressed. Furthermore, baseline resting state connectivity within the orbitofrontal component of the DMN, namely in the bilateral anterior cingulate regions, was a significant a predictor of clinical response.

Normalization of limbic hyper-responsiveness has been commonly reported in MDD [3-5] and appears to be specific to sad facial expressions [34]. However, we did not observe increased amygdala activation to sad faces in the acutely depressed MDD participants nor any significant group by time effects following treatment. Potential confounds include factors related to the sample and task. In the present group, the depressive symptoms was of a moderate to severe severity which is comparable to previous samples in which increased amygdala responses have been observed [3-5,34]. The present task used implicit affective processing in order to increase the potential to engage amygdala responsivity, while a masked presentation may have more fully captured amygdalar automatic processing [35,36], and the number of subjects and the design of the task, which was an event-related design rather than a blocked design, may have limited the power to observe a significant effect [35]. Furthermore, most studies to date have examined the effects of the SRI class of antidepressants [3-5,34]. Single doses of SRI medications in healthy participants have been associated with decreased amygdala responses to emotional faces, while single-dose NRIs lead to increased activation in medial and frontal regions [11]. It is unclear whether the effects of different classes of antidepressants are comparable as it has been proposed that SRIs have an early attenuating effects on emotional reactivity while NRIs have a more modulatory effect on attention regulation of emotional processes and may not necessarily have a direct impact on amygdala responsivity which would be observed in addition to potential state effects related to acute depressive states as compared to states of remission [9-11,37].

In order to examine the negative attention bias in MDD [38], we applied an emotional Stroop task [24,39]. We found a significant interaction effect in the posterior cingulate cortex in which increased baseline activation in MDD showed a linear normalization with successive measures following treatment as compared to healthy participants who underwent the same scans. The posterior cingulate cortex is involved in the DMN, which has a central role in many situations whereby attention is internally directed such as in episodic memory retrieval and inner

reflection [40]. Increased posterior cingulate activation in MDD patients while acutely depressed may be understood as reflecting a failure to attenuate self-referential activity, perhaps leading to interference in task performance. With treatment, attenuation of posterior cingulate activity may reflect an improvement in selective attention and the ability to focus.

In parallel, the resting-state functional connectivity in MDD patients showed increased connectivity over the course of treatment within the anterior DMN in the subgenual anterior cingulate and regions involved in attention-processing, namely the superior frontal and parietal cortices, while reduced connectivity was observed in the prefrontal regions linked to the DMN. Anand *et al.* [41] also found increased connectivity with the anterior cingulate and limbic regions following treatment with a variety of antidepressant medications, and Li *et al.* [42] have proposed that persistent increased functional connectivity in anterior DMN reflects a trait effect of MDD and a potential risk for relapse.

The present findings bring into question the potential for amygdala responsivity as a state marker of MDD because no significant differences were found during an acute episode or following 12 weeks of treatment in which the majority of patients' symptoms fulfilled criteria for clinical remission reflecting the numerous factors which impact on amygdala responsivity [35]. Rather the negative affective bias appears to have been more strongly detected by the emotional attention processing task which revealed a significant group by time effect with normalization of activation in the posterior cingulate. The corresponding increase in resting state connectivity in MDD patients with treatment highlights potential links between the negative affective bias that is characteristic of MDD and the resting state network [37]. Moreover, there are persuasive indications that these effects may be related to the NRI class of antidepressant medication [9-12,37] although this requires further investigation.

As a potential marker of clinical response, we found that MDD patients with reduced functional connectivity with the subgenual anterior cingulate showed the greatest clinical improvement following treatment. The subgenual anterior cingulate has a key role in MDD [43], and activity in this region has been consistently implicated as a predictor of clinical response [7,44]. Increased functional connectivity with the subgenual anterior cingulate has been associated with increased length of illness [45], and the neuropsychological mechanisms of rumination and brooding have been correlated with increased connectivity between the subgenual anterior cingulate and posterior cingulate [46], including in treatment-naïve MDD patients with increased functional connectivity in the medial prefrontal and subgenual anterior cingulate [47]. Anterior cingulate-limbic white matter tracts have also been predictive of clinical response [48], though the degree to which white matter tract structural connectivity form the basis of resting state functional connectivity requires further validation [49].

From the MMRM model, an early increase in left hippocampal volume after 1 week of treatment predicted subsequent clinical response. Although the volume change was small, the high intraclass correlations in hippocampal volumes with the repeated measures in the healthy participants indicate a high reliability of the measure. Sämann [50] reported that increased left hippocampal gray matter volume was predictive of treatment response to a variety of antidepressant medications, and our meta-analysis supported the observation of reduced right hippocampal volume being predictive of a poorer clinical response [7]. Increases in hippocampal volume have been observed following short term [51] and long term [52] treatments with antidepressant medications. Our finding suggests that antidepressant medications can increase hippocampal volume early in the course of treatment, such increases may be predictive of clinical response, and provides some corroboration for hippocampal neurogenesis as a mechanism for the effects of antidepressant therapy [53].

Limitations

The high response rate in this open study though has limited the power to detect differences between responders and MDD patients with a more treatment-resistant form of depression, which may be associated with distinct neural correlates [41]. The absence of a placebo-control treatment arm limits our attribution of effects to the antidepressant medication as opposed to changes associated with clinical improvement, although possible confounds of time were accounted for by healthy participants having the same serial scans. Furthermore, we did not find any significant differences between MDD patients and healthy participants in response to the happy and sad faces stimuli, perhaps in part reflecting the poor test-retest reliability of amygdala response to these emotional faces [54], while resting-state fMRI data show greater robustness and reproducibility [55]. Test-retest reliability of a neuroimaging measure becomes particularly important in the development of biomarkers for prognosis and diagnosis [44].

Conclusions

In summary, multimodal functional and structural neuroimaging correlates demonstrated significant effects of treatment in the anterior DMN associated with resting state connectivity and in response to negative attentional biases, but not in response to happy or sad facial expressions. Moreover, anterior cingulate functional connectivity predicted clinical response. Our findings reflect the distinct effects of the SNRI class of antidepressants as well as

methodological factors of test-retest reliability and reproducibility of fMRI tasks. Further investigation is required to examine the specificity of the SNRI effects.

Availability of supporting data

The data sets supporting the results of this article are included within the article and its additional files.

Additional file

Additional file 1: Supplementary Methods and Results.

Abbreviations

BOLD: Blood oxygenation level-dependent; CGI-S: Clinical Global Impression of Severity; DMN: Default mode network; DSM-IV-TR: *Diagnostic Statistical Manual of Mental Disorders*, Fourth edition, text revision; FWE: Family-wise error; fMRI: Functional magnetic resonance imaging; FSL: FMRIB Software Library; HAMA: Hamilton Anxiety Rating Scale; HRSD-17: 17-item Hamilton Depression Rating Scale; IQ: Intelligence quotient; MDD: Major depressive disorder; MELODIC: Multivariate Exploratory Linear Optimized Decomposition into Independent Components; MMRM: Mixed-effects model repeated measures; MRI: magnetic resonance imaging; NRIs: Norepinephrine reuptake inhibitors; SCID-IV: Structured Clinical Interview for DSM-IV Axis I disorders; SDS: Sheehan Disability Scale; sMRI: Structural magnetic resonance imaging; SNRI: Serotonin-norepinephrine reuptake inhibitor; SRIs: Serotonin reuptake inhibitors.

Competing interests

The study was funded by Eli Lilly and Company. CHYF and SGC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CHFY has final responsibility for the decision to submit for publication. CHYF and MMR have held recent research grants from Eli Lilly and Company and GlaxoSmithKline and have received consulting fees from Eli Lilly, Roche, Sunnovion, Stroke-Med. SGC, AS, TMA, LAM, and PH report no potential conflicts of interest. RD and MMR report ownership interest in Pax Neuroscience, and MMR reports partial salary support via a Merit Award from the Veterans Administration. PL is full-time employee and stockholders of Eli Lilly and Company. LBM was a former employee and stockholder of Eli Lilly and Company.

Authors' contributions

CHYF, SGC, LBM, and MMR made substantial contributions to conception and design of the study. CHYF, SGC, AS, and TMA made substantial contributions to the acquisition of data. CHYF, SGC, PL, AS, TMA, LAM, and PH made substantial contributions to the data analysis. CHYF, SGC, LBM, MMR, and RD made substantial contributions to the interpretation. All authors contributed to revising the manuscript critically for important intellectual content and final approval.

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